Korean Journal of Pediatrics Vol. 52, No. 11, 2009
DOI : 10.3345/kjp.2009.52.11.1279
■ Case report ■

Hepatic glycogenosis in a patient with poorly controlled type 1 diabetes mellitus

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= Abstract =

Hepatomegaly and liver dysfunction might develop in patients with diabetes mellitus due to glycogen deposition or nonalcoholic steatohepatitis. We experienced a case of hepatic glycogenosis in a patient with type 1 diabetes mellitus who presented with recurrent hypoglycemia, suggesting impairment of glycogenolysis and gluconeogenesis. A 10-year-old girl with a 4-year history of type 1 diabetes mellitus was admitted because of recurrent hypoglycemia and abdominal pain in the right upper quadrant. She had Cushingoid features and hepatomegaly that extended 6 cm below the right costal margin. Laboratory data and radiologic examination revealed elevated liver enzyme levels due to fatty liver. Periodic acid-Schiff (PAS) staining revealed intense glycogen deposition in the cytoplasm of the hepatocytes and PAS reactivity was lost with diastase treatment. At 2 months after administration of glucagon injection and uncooked cornstarch between meals and at bedtime, the hypoglycemic episodes and liver dysfunction improved. It is important to distinguish hepatic glycogenosis from steatohepatitis, because it is possible to prevent excessive hepatic glycogen storage in hepatic glycogenosis cases by strictly controlling blood glucose level and by glucagon administration. To prevent severe hypoglycemic symptoms accompanied by hepatic glycogenosis, we suggest that uncooked cornstarch, which is effective in maintaining blood glucose level, can also be administered. (Korean J Pediatr 2009;52:1279-1282)

Key Words : Starch, Glucagon, Hypoglycemia, Diabetes mellitus, Type 1

Introduction

Hepatomegaly and hepatic dysfunction in patients with diabetes mellitus can be caused by excessive hepatic glycogen deposition or nonalcoholic steatohepatitis (NASH). The frequency of hepatic glycogenosis in patients with type 1 diabetes mellitus is relatively rare in children who undergo insulin therapy. The clinical features of hepatic glycogenosis in type 1 diabetes mellitus are hepatomegaly, hypoglycemia, elevated transaminase, hyperlipidemia and ketosis[1]. It is important to distinguish between hepatic glycogenosis and NASH, because hepatic glycogenosis can be reversed by strict blood glucose control and glucagon injection, whereas for the latter this is not possible. Moreover, NASH is a progressive disease that may lead to fibrosis or cirrhosis of the liver, while hepatic glycogenosis is not known to cause fibrosis or cirrhosis[1, 2]. We experienced a case of hepatic glycogenosis in a girl with poorly controlled type 1 diabetes mellitus who presented with recurrent hypoglycemia and hepatomegaly, which suggested impaired glycogenolysis and gluconeogenesis.

Received : 6 May 2009, Revised : 17 July 2009
Accepted : 22 September 2009
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Case report

A 10-year-old girl, who was diagnosed with type 1 diabetes mellitus at 6 years of age, was admitted because of recurrent hypoglycemia and right upper quadrant pain. She had been treated with a conventional insulin regimen consisting of combinations of intermediate- and rapid-acting insulin preparations. However, hyperglycemia and hypoglycemia occurred alternately during daytime as well as nighttime due to poor compliance and irregular insulin

injection. On admission, her height was 132.1 cm (25-50 percentile) with a weight of 33.9 kg (75-90 percentile). She had Cushingoid features and hepatomegaly extending 6 cm below the right costal margin. Laboratory data showed glycosylated hemoglobin (HbA1c) 9.6%, aspartate aminotransferase (AST) 321 U/L, alanine aminotransferase (ALT) 481 U/L, total cholesterol 250 mg/dL, triglyceride 267 mg/dL, and positive urine ketone; however, serum total bilirubin, albumin, alkaline phosphatase, γ-glutamyl transpeptidase, lactate dehydrogenase, prothrombin time, and thyroid hormone levels were normal. Serological examinations for viral hepatitis, autoimmune hepatitis and metabolic liver disease were negative. Abdominal ultrasound revealed fatty liver and hepatomegaly. Liver biopsy revealed preservation of the hepatic microlobular architecture. Periodic acid Schiff (PAS) staining revealed many PAS-positive granules within the cytoplasm of hepatocyte (Fig. 1A). PAS staining following digestion with diastase (D-PAS) demonstrated that the granules had disappeared, confirming the presence of glycogen in hepatocyte cytoplasm (Fig. 1B). Electron microscopic findings showed diffuse glycogen particles with dislocated and atrophic mitochondria in the cytoplasm of hepatocytes. The insulin regimen was changed to multiple daily injections consisting of 6 units of insulin lispro before meals and 6 units of insulin glargine before bedtime, and 50 g of uncooked cornstarch was given between meals and bedtime. Diet plan consisted of approximately 2,000 calories per day, divided into 60% carbohydrate, 20% fat, and 20% protein. The distribution was in 3 meals and uncooked cornstarch in 3 snacks, a snack being approximately 10% of the daily calories. Severe hypoglycemic symptoms, such as seizures and drowsy mental changes, were controlled by glucagon injection. The patient needed glucagon injections 7 to 8 times a day initially. After 2 months, the number of hypoglycemic episodes (blood glucose less than 60 mg/dL) decreased with intensive insulin therapy and uncooked cornstarch, and the number of glucagon injections decreased to 1 or 2 times a day. The side effects of cornstarch ingestion such as diarrhea, abdominal distention, and increased flatulence were not seen in this patient. Laboratory findings showed decreased transaminase levels (AST 46 IU/L, ALT 51 IU/L) and HbA1c level (8.4%). However, hepatomegaly had not been improved after 2 months of treatment.

Discussion

Long-standing hyperglycemia, overinsulinization, glucose given to control hypoglycemia, and increased concentrations of the counterregulatory hormones are the risk factors for hepatic glycogenosis in patients with type 1 diabetes mellitus by their concerted actions on the glycogen phosphorylase and synthase enzymes[3-5]. In 1930, noticeable hepatomegaly due to excessive hepatic glycogen accumulation and hepatic dysfunction in patients with poorly controlled type 1 diabetes mellitus was identified and referred to as Mauriac syndrome[6]. So far, three cases of Mauriac syndrome have been reported in the literature in Korea[7-9]. A typical Mauriac syndrome presents pro-

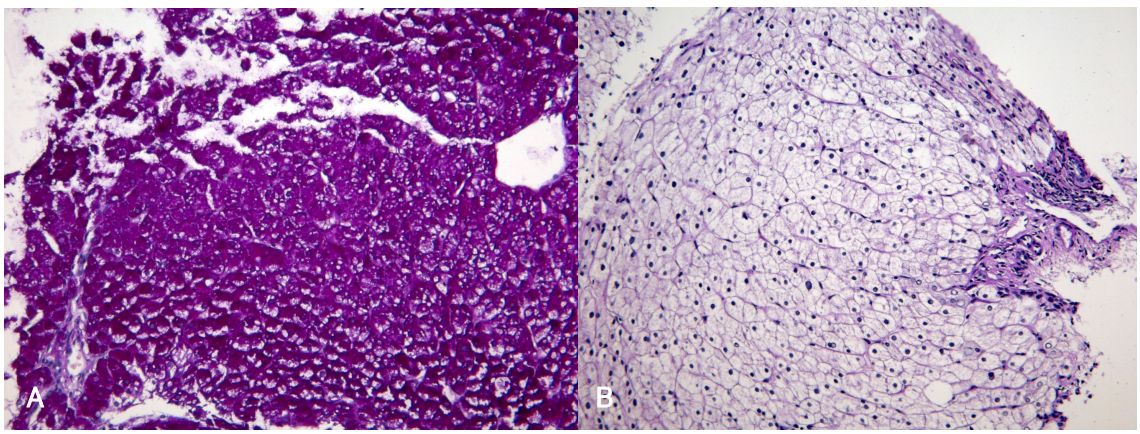

Fig. 1. Histological findings of liver biopsy. (A) Periodic acid-Schiff (PAS) staining reveals intense reaction in the cytoplasm of hepatocytes (PAS without diastase, ×200). (B) PAS staining after diastase treatment demonstrates complete absence of the reaction (D-PAS stain, ×200).

found growth retardation in addition to poorly controlled diabetes, hepatic dysfunction. However, our case is not associated with dwarfism and delayed bone age, which is different from typical Mauriac syndrome. Hepatic glycogenosis in patient with uncontrolled diabetes occurs as a result of passive flux of glucose into hepatocyte. Glucose is converted into glucose-6-phosphate by glucokinase. Then glucose-6-phosphate is converted into glycogen by glycogen synthase. Glycogen synthase exist in an inactive (phosphorylated) and active (dephosphorylated) form. The conversion of inactive form into active form is controlled by phosphatase. Long-term hyperglycemia, irregular insulin injection and large doses of glucose administered to correct the recurrent hypoglycemia result in increased phosphatase concentration, which lead to glycogen synthesis and accumulation[4]. Decreased glycogenolysis is also a cause of hepatic glycogenosis. Phosphorylase kinase activate glycogen phosphorylase, which is associated with glycogenolysis. However, prolonged hyperglycemia leads to inactivation of phosphorylase kinase[10]. Hepatic glycogenosis can also occur as one of the early manifestations in type 1 diabetes mellitus[11]. In adults with type 1 diabetes mellitus, two cases of hepatic glycogenosis have been reported in Korea[10, 12]. However, this is the first case of hepatic glycogenosis in a child with type 1 diabetes mellitus in Korea. Hepatic glycogenosis in type 1 diabetes mellitus is a benign disease with little chance of progression to fibrosis or cirrhosis, and readily treatable by improvement of glycemic control in a few weeks to months. Minimum dosage of insulin and glucagon injection is required for regression of hepatomegaly and better metabolic control[5]. To prevent severe hypoglycemic symptoms accompanied by hepatic glycogenosis, uncooked cornstarch can be used and was effective in maintaining blood glucose concentrations. Uncooked cornstarch has been studied extensively in glycogen storage disease and diabetes mellitus. There have been several reports that used uncooked cornstarch as a bedtime snack to prevent nocturnal hypoglycemia in patients with type 1 diabetes mellitus[13-15]. When hypoglycemia becomes prolonged, the use of glucagon will reduce the amount of glucose administered, and perhaps reduce the amount of glycogen stored in the liver[5]. It is unusual to use multiple glucagons injections per day. However, glucagon injections were inevitable because of severe hypoglycemic symptoms including mental change and seizures. In this case, recurrent hypoglycemic symptoms were improved by uncooked cornstarch and glucagon injections. The etiology of susceptibility to excessive liver glycogen storage in patients with type 1 diabetes is not clarified yet. However, it should be considered that patients with poorly controlled type 1 diabetes mellitus manifesting recurrent hypoglycemia, hepatic dysfunction and hepatomegaly might have reversible hepatic glycogenosis. Strict blood glucose control and prevention of hypoglycemia is needed to reverse hepatomegaly and improve hepatic dysfunction.

한 글 요 약

혈당 조절이 불량한 제1형 당뇨병 환자에서 발생한 간의 당원축적증

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당뇨병 환자에서 간비대와 간 기능 이상이 동반될 경우 간 내 당원축적증과 비알콜성 지방간염을 감별해야 한다. 저자들은 인슐린 치료를 제대로 받지 않아 혈당 조절이 불량한 환자에서 저혈당과 간비대로 발현한 간 내 당원축적증을 경험하여 보고한다. 만 6세경 1형 당뇨병으로 진단받은 환아로 10세경 우상복부 통증과 반복되는 고혈당과 저혈당으로 내원하였으며, 당시 진찰상 둥근 얼굴, 우측 늑골연 하방 6 cm 정도에서 만져지는 간비대가 있었다. 검사상 소변 케톤 양성, 당화혈색소는 9.6%였다. 간 효소치가 증가되어 있었고, 혈중 콜레스테롤/중성지방 250/267 mg/dL였다. 바이러스성 간염, 자가면역성 간염, 대사성 간 질환에 대한 검사는 모두 정상이었다. 복부 초음파 및 컴퓨터 단층 촬영상 지방간과 간비대 소견을 보였다. 간 조직 검사상 PAS 염색에서 양성, diastase-PAS 염색에서는 음성으로 전형적인 당원축적증의 소견을 보였다. 고혈당을 보일 때마다 초속효성 인슐린을 투여하고 심한 저혈당의 증상이 동반된 경우 글루카곤을 투여하였으며 생옥수수 전분 가루를 간식으로 먹이면서 저혈당 횟수가 감소하여 퇴원하였다. 현재 외래에서 초속효성 인슐린으로 혈당 조절하면서 관찰 중이다. 제1형 당뇨병 환자에서 당원축적증은 간비대와 간 효소치의 상승을 야기할 수 있는 원인이다. 본 증례에서는 심한 저혈당이 반복되어 하루에도 수 차례 글루카곤을 투여하였으며, 생옥수수 전분 가루을 투여하면서 저혈당이 호전되었다. 엄격한 혈당 관리로 간 비대 및 간 기능 이상이 호전될 수 있으므로 적절한 인슐린 치료로 혈당을 조절하고 저혈당을 예방해야 하겠다.

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