Glycogenic Hepatopathy in Type 1 Diabetes Mellitus

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Abstract:
Glycogenic hepatopathy (GH) is a rare complication of poorly controlled type 1 diabetes mellitus (T1DM), and is characterized by elevated liver enzymes, hepatomegaly, and glycogen accumulation. We herein present the case of a 23-year-old man with poorly controlled T1DM who had liver dysfunction. Imaging studies showed severe hepatomegaly and fatty liver. The examination of a liver biopsy specimen revealed fatty droplets, ballooning, inflammation, and mild fibrosis. Subsequent periodic acid-Schiff (PAS) staining after diastase digestion confirmed GH. In this case, the improvement of hyperglycemia, not HbA1c, resulted in the improvement of the patient’s liver function. This is the first report on the use of continuous glucose monitoring in patients with GH to show that continuous hyperglycemia may worsen GH.

Key words: glycogenic hepatopathy, poorly controlled type 1 diabetes mellitus, periodic acid-Schiff staining, hepatomegaly

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Introduction

Glycogenic hepatopathy (GH) was first identified by Mauriac in 1930 (1), and is characterized by elevated liver enzymes, hepatomegaly, and glycogen accumulation in hepatocytes. GH is a relatively rare complication of poorly controlled type 1 diabetes mellitus (T1DM) (2). The etiology of GH has not been completely clarified. GH is not well recognized by general physicians, and is usually misdiagnosed as nonalcoholic fatty liver disease (NAFLD) because it is difficult to differentiate GH from NAFLD based on imaging examinations. In addition, even if a liver biopsy is performed, it is difficult to distinguish GH from NAFLD with Hematoxylin and Eosin (H&E) staining alone. To diagnose GH correctly, it is necessary to perform periodic acid-Schiff (PAS) staining before and after diastase digestion. The standard treatment for GH is the improvement of glycemic control; in some cases, GH improves without the improvement of the HbA1c level. GH may have a good prognosis, with the complete resolution of symptoms and the normalization of the liver function (3).

Case Report

A 23-year-old man was referred to our hospital to undergo treatment for poorly controlled T1DM and an investigation to determine the cause of liver dysfunction. He was diagnosed with T1DM at another hospital at 6 years of age, after which he started intensive insulin therapy. As his blood glucose level was poorly controlled, he was admitted to hospital several times due to diabetic ketoacidosis. Since 16 years of age, his transaminase levels had sometimes become elevated. His liver dysfunction continued and a liver biopsy was performed at 20 years of age, which revealed hepatocytes with fatty droplets, ballooning, mild inflammation, and mild fibrosis in the portal region. At this time, he was diagnosed with NAFLD, and treatment with ethyl eicosapentaenoic acid and bezafibrate was initiated. His transaminase levels remained elevated and at 23 years of age he was re-
ferred to our hospital for the treatment of T1DM and to undergo an investigation to determine the cause of liver dysfunction.

On the patient’s first visit to our hospital, his height was 168.8 cm, his body weight was 64 kg, and his body mass index was 22.4 kg/m². He reported that he did not smoke or drink alcohol. The laboratory data were as follows: aspartate aminotransferase (AST), 83 U/L; alanine aminotransferase (ALT), 44 U/L; total cholesterol, 188 mg/dL; triglyceride, 150 mg/dL; fasting blood glucose, 225 mg/dL; HbA1c, 12.9%; and self-measured blood glucose showed brittle diabetes. Despite an increase in insulin (insulin glulisine 14 U before meals in the morning and 12 U at noon and in the evening, and insulin glargine 16 U at bedtime), his glycemic control remained poor (HbA1c, 11.5-12.9%) and his transaminase levels continued to fluctuate.

Three months after his initial visit to our hospital, his transaminase levels showed sudden elevation with no obvious symptoms. Thus, he was admitted due to the suspicion of acute hepatitis. The laboratory data on admission are shown in Table. Ultrasonography and contrast-enhanced computed tomography showed severe hepatomegaly and fatty liver (Fig. 1, 2A and B). However, his transaminase levels continued to fluctuate.

Figure 1. (A, B) Ultrasound images showing severe hepatomegaly and fatty liver.
and bezafibrate were negative, and we did not suspect drug-induced liver injury. Liver biopsy was performed on the 17th day of admission in order to investigate the pathogenesis of his liver dysfunction. H&E and azan staining revealed slight inflammation of the portal area, slight intralobular ballooning of the hepatocytes, and mild pericellular fibrosis, without piecemeal necrosis or expanding fibrosis (Fig. 3). Thus, steatohepatitis was suspected based on the histological findings. The patient was discharged on the 19th day of admission.

After discharge, his transaminase levels remained high (AST/ALT, 100-200 U/L). At five months after discharge, his transaminase levels showed remarkable elevation for the second time (AST/ALT, 1,115/593 U/L), with no obvious symptoms. As his clinical course was inconsistent with that of NAFLD, we suspected GH, and added PAS staining before and after diastase digestion to the last liver biopsy specimen. PAS staining revealed many PAS-positive granules within the cytoplasm of the hepatocytes (Fig. 4A), while PAS staining after diastase digestion showed the disappearance of such granules (Fig. 4B). GH was finally diagnosed based on these histological findings.

As GH is usually caused by poorly controlled T1DM, we changed insulin glargine 21 U to insulin degludec 21 U, with the aim of improving the patient’s glycemic control. Although his HbA1c did not change, his transaminase levels
Figure 4. Periodic acid-Schiff (PAS) staining of the liver biopsy specimen. (A) Many PAS-positive granules were observed within the cytoplasm of the hepatocytes (magnification ×40). (B) The disappearance of PAS-positive granules after diastase digestion (magnification ×40).

Figure 5. Changes of AST, ALT, and GGT.

showed an improvement of the liver function (Fig. 5). Continuous glucose monitoring also showed the improvement of the peak glucose level. Currently, his fatty liver and hepatomegaly have improved and his liver function has remained stable (Fig. 2C and D).

Discussion

GH was first described in 1930 as part of Mauriac syndrome, which includes growth retardation, hepatomegaly, cushingoid features, and delayed puberty (1). Currently, GH is known to be a rare complication of poorly controlled T1DM (2). The pathologic findings of GH include the accumulation of glycogen in hepatocytes (4), which manifests when extrahepatic glucose is in equilibrium with intrahepatic glucose. As the blood glucose level increases above a certain threshold, glucokinase begins to produce glucose 6-phosphate, which binds to liver glycogen synthase, causing allosteric activation. Then, glycogen synthesis is activated. Thus, a hyperglycemic state with poorly controlled T1DM causes the excessive synthesis of glycogen (5). In addition to this, Munns et al. (6) suggested that patients with poorly controlled T1DM often develop hypoglycemia by taking excess insulin, and treat this state with the administration of glucose, which is considered to be a mechanism of overglycogenosis. However, not all patients with poorly controlled T1DM develop GH. It has been suggested that some regulatory protein is responsible for the marked accumulation of glycogen. Tomihira et al. (7) reported that the partial inhibition of liver glycogen phosphorylase may induce GH. These authors sequenced the gene encoding phosphorylase, but could not detect the gene. Thus, the mechanism of GH has
not been fully clarified.

The most common clinical findings in GH are elevated liver enzymes, hepatomegaly, and fatty liver (8). Based on these characteristics, the clinical course of our patient is compatible with that of GH. However, he was initially diagnosed with NAFLD based on the liver histology. Although it is difficult to differentiate GH from NAFLD, it is important to diagnose GH correctly because their prognoses are different. The prognosis of GH is suspected to be good as long as adequate glycemic control is achieved (9). On the other hand, NAFLD may cause inflammation and lead to nonalcoholic steatohepatitis (10), or progress to advanced liver cirrhosis or hepatocellular carcinoma (11). However, it is difficult to distinguish GH from NAFLD in a liver biopsy specimen based on H&E staining alone. Thus, PAS staining before and after diastase digestion is helpful for the diagnosis of GH. We suggest that clinicians should consider GH when liver dysfunction, hepatomegaly, and fatty liver are found in a patient with poorly controlled T1DM, and that they should perform liver biopsy with PAS staining before and after diastase digestion.

In previous reports, there have been some cases in which the liver dysfunction of GH was improved by the intensification of glycemic control, especially with the improvement of HbA1c (11-14). Ikarashi et al. (15) also reported four cases of GH, in which the HbA1c level on admission was markedly high (11.0-16.5%), and in which the improvement of HbA1c by strict glycemic control resulted in the improvement of liver dysfunction. However, in comparison to 2 diabetes mellitus, glycemic control can be more difficult in T1DM. In our case, although we tried to improve glycemic control in cooperation with a diabetes expert, the patient’s HbA1c showed no improvement. Nevertheless, his transaminase levels improved after insulin glargine was changed to insulin degludec. Our case showed a decreased range of postprandial glucose increase, an improved peak glucose level, and less time in a remarkable hyperglycemic state. The effects of the transition of glucose using continuous glucose monitoring for GH have not been reported. Similarly to our case, Cha et al. (16) reported 3 cases of GH that showed an improvement of the liver function without an improvement of HbA1c. Another recent study showed that the range of the postprandial glucose increase in patients with T1DM were significantly different between meals in patients taking insulin glargine but that the range between meals did not differ to a statistically significant extent in patients taking insulin degludec (17). These findings suggest the improvement of peak glucose level or remarkable continuous hyperglycemic state, rather than the improvement of the HbA1c (average blood glucose) level is important for the improvement of GH. This is the first report to show that continuous glucose monitoring for GH and the improvement of the peak glucose level may improve GH.

**Conclusion**

When encountering patients with T1DM who present with liver dysfunction, hepatomegaly, and fatty liver, clinicians should consider GH, and perform liver biopsy with PAS staining before and after diastase digestion in order to diagnose GH correctly. Continuous glucose monitoring may help in the treatment of GH.

**The authors state that they have no Conflict of Interest (COI).**

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