A case of glycogenic hepatopathy developed in a patient with new-onset fulminant type 1 diabetes: the role of image modalities in diagnosing hepatic glycogen deposition including gradient-dual-echo MRI


1) Department of Metabolism/Diabetes and Clinical Nutrition, Nagasaki University Hospital, Nagasaki 852-8501, Japan
2) Department of Internal Medicine, National Hospital Organization Saga National Hospital, Saga 849-8577, Japan
3) Department of Molecular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8523, Japan
4) Department of Endocrinology and Metabolism, Nagasaki University Hospital, Nagasaki 852-8501, Japan
5) Department of Radiology, Nagasaki University Hospital, Nagasaki 852-8501, Japan
6) Center for Health and Community Medicine, Nagasaki University, Nagasaki 852-8521, Japan

Abstract. Glycogenic hepatopathy (GH) has been reported as a very rare and under recognized complication in long-standing poorly controlled type 1 diabetes (T1D) patients. GH is characterized by transient elevation of liver transaminase and hepatomegaly caused by reversible and excessive glycogen accumulation in hepatocytes. It has been reported that GH is indistinguishable from non-alcoholic fatty liver disease, which is more commonly seen in diabetic patients, even after a thorough clinical history is taken or careful physical examination or imaging studies are performed. GH can only be diagnosed by liver biopsy. We here demonstrate a 21-year-old male patient with new-onset fulminant T1D complicated with diabetic ketoacidosis who subsequently developed GH just after the initiation of insulin treatment. The marked liver dysfunction (serum levels of aspartate aminotransferase 769 IU/L and alanine aminotransferase 1348 IU/L) and hepatomegaly improved spontaneously via glycemic control without any specific treatments thereafter. Moreover, the insulin requirement dramatically decreased from 168 to 80 units per day as GH improved, suggesting a potential role of GH in insulin resistance. GH was diagnosed based on the histological findings of the liver in our case, but we were able to predict GH before the biopsy based on the findings in the gradient-dual-echo magnetic resonance imaging sequence combined with ultrasound and/or computed tomography examinations of the liver.

Key words: Glycogenic hepatopathy, Glycogen, Fulminant type 1 diabetes, Hepatomegaly, Magnetic resonance imaging (MRI)

GLYCOGENIC HEPATOPATHY (GH) is a very rare complication seen mostly in patients with type 1 diabetes (T1D) in whom glycemic control has been poor for a long time [1-12]. GH is characterized by a transient liver dysfunction associated with hepatomegaly caused by reversible and excessive glycogen accumulation in the hepatocytes. GH has been known to be indistinguishable from non-alcoholic fatty liver disease (NAFLD), which is more commonly seen in diabetic patients, even after a thorough clinical history is taken or careful physical examination or imaging studies are performed [1-8]. Therefore, the diagnosis of GH has only been made by means of a liver biopsy in the previous reports [1-8]. We report the first case of GH developed in a patient with diabetic ketoacidosis caused by new-onset fulminant T1D. Although the definitive diagnosis of GH was made histologically, a potential use of gradient-dual-echo magnetic resonance imaging (MRI) study of the liver [13, 14] in the diagnosis of GH is also discussed.
Case

A 21-year-old male was admitted to a regional hospital because of cardiopulmonary arrest that had developed at home. He had been healthy with no particular medical history. He had been suffering from severe general fatigue, thirst, and polyuria for a few days before he developed cardiopulmonary arrest. An electrocardiogram taken upon arrival of the ambulance showed ventricular tachycardia, and the arrhythmia was terminated using an automated external defibrillator. Blood tests showed marked metabolic acidosis (pH 7.15 and HCO3- 8.1 mEq/L) associated with a remarkably high plasma level of glucose (1495 mg/dL) and high serum ketone (481 µmol/L), compatible with diabetic ketoacidosis (DKA). He was treated with continuous intravenous injection of regular insulin along with massive infusion of saline. Despite the marked hyperglycemia detected upon admission, HbA1c (NGSP) was 6.2 %, suggesting an extremely rapid onset of hyperglycemia. The serum level of C-peptide was exhausted (0.04 ng/ml), and anti-islet autoantibodies (Abs), including glutamic acid decarboxylase Abs, insulinoma-associated antigen-2 Abs and insulin Abs, were not detected in his sera. Therefore, he was diagnosed with fulminant T1D based on the diagnostic criteria of the Japan Diabetes Society [15].

A few days after the successful treatment of DKA, he was able to ingest food under treatment with multiple injections of insulin aspart and insulin glargine. The patient was transferred to Nagasaki University Hospital for further treatment and education about diabetes (Fig. 1). Upon admission to our university hospital, we found that the patient had moderate liver dysfunction, with serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 119 IU/L and 122 IU/L, respectively, without apparent hepatosplenomegaly, and, therefore, we considered the liver dysfunction of the patient to be due to a shock liver caused by DKA and cardiopulmonary arrest. However, there was a subsequent appearance of marked hepatomegaly, palpable 2 cm below the right costal margin, associated with the progression of the liver dysfunction indicated by increasing serum levels of AST (769 IU/L) and ALT (1348 IU/L) (Fig. 1). Serological tests excluded hepatic viral infection caused by hepatitis A, B, or C, Epstein-Barr virus, or cytomegalovirus, and autoantibody examination in the sera made autoimmune hepatitis and primary biliary cirrhosis unlikely. Ultrasound examination of the liver showed a mild bright liver (Fig. 2A), and abdominal computed tomography (CT) showed hepatomegaly with diffuse low density (43 HU, Fig. 2C), suggesting a fatty liver. However, it was extremely difficult for us to consider NAFLD as a cause of the progressive hepatomegaly and marked liver dysfunction in our patient who was a slender build (175.3 cm high, 55.8 kg in weight) and receiving the standard nutrition provided by the hospital. In order to evaluate fat deposition in the liver, the patient underwent an MRI study which demonstrated only a subtle difference in the signal intensities between in-phase (Fig. 3A) and opposed-phase images of the liver (Fig. 3B) in the T1-weighted gradient dual-echo sequence, suggesting that intrahepatic fat accumulation was unlikely [13, 14]. This finding was further supported by the liver biopsy finding. We were able to find few fat droplets in the hepatocytes and no apparent inflammatory cell infiltration or fibrosis. The hepatocytes were found to be diffusely swollen, and some hepatocytes showed empty nuclei with ring-like chromatin elements (Fig. 4A), so-called glycogen nuclei. The cytoplasm of the hepatocytes was densely stained with Periodic Acid-
Fig. 2  Ultrasound and CT findings in the liver
Ultrasound examinations of the liver performed on the ninth day (A) and at the liver biopsy on the nineteenth day (B). The sonographic intensity was decreased in the liver on the CT (C) taken on the ninth day. It should be noted that a mild bright liver can be similarly observed in (A) and (B).

Fig. 3  Gradient-dual-echo MRI examinations in the liver
T1-weighted gradient-dual-echo MRI images recorded with in-phase (A) and opposed-phase (B) conditions performed prior to liver biopsy. Generally fat contents are obtained from images in which the signal intensity at in-phase is greater than that at opposed-phase. However, there is no significant difference in the signal intensities between the two images; thus, these findings were not consistent with intrahepatic lipid storage.
GH was first described in children with brittle diabetes by Mauriac in 1930 as part of Mauriac syndrome including growth retardation, hepatomegaly, cushingoid features and delayed puberty [16]. Marked hepatomegaly and the elevation of transaminases are characteristic findings in GH as a result of intrahepatic glycogen storage. Histologically, GH is characterized by several features: 1) marked glycogen accumulation leading to pale, swollen hepatocytes; 2) no or mild fatty change; 3) no or minimal inflammation; 4) no or minimal spotty lobular necrosis; and 5) intact architecture with no significant fibrosis [1].

GH tends to occur in patients with poorly controlled T1D, especially in children and adolescents (Table 1) [1, 2, 4, 6-12]. GH has also been reported in patients with poorly controlled type 2 diabetes (T2D) treated with insulin therapy [17], as well as in a T2D patient who injected 180 units of insulin glargine as suicide...
Glycogenic hepatopathy in fulminant T1D

In patients exposed to either excessive insulin and/or enormous amounts of glucose. Although the underlying mechanisms by which GH develops are not fully clarified, wide fluctuations both in glucose and insulin levels seem to be essential in its pathophysiology. For example, in a patient presently developing T1D, high plasma glucose levels cause an insulin-independent glucose influx into the hepatocytes, which induces attempt and treated with intravenous hypercaloric infusion for three days (Table 2) [18]. In addition, GH has been reported in a toddler with dumping syndrome associated with gastrostomy feeding without glucose intolerance [19], and in three children without diabetes under high-dose glucocorticoid treatments (Table 2) [20]. Therefore, GH seems to develop not only in T1D patients controlled poorly for a long term but also in patients exposed to either excessive insulin and/or enormous amounts of glucose. Although the underlying mechanisms by which GH develops are not fully clarified, wide fluctuations both in glucose and insulin levels seem to be essential in its pathophysiology. For example, in a patient presently developing T1D, high plasma glucose levels cause an insulin-independent glucose influx into the hepatocytes, which induces

Table 1  T1D patients with glycogenic hepatopathy diagnosed based on histological findings: summary of representative English literatures including ours.

<table>
<thead>
<tr>
<th>Age (years)/Sex</th>
<th>Diabetic control</th>
<th>Hepatomegaly</th>
<th>Peaks of AST/ALT (IU/L)</th>
<th>The image finding of GH (image modalities)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-34 (19.9±6.6)/M9:F5 (n=14)</td>
<td>Poor for a long time in all cases</td>
<td>+ (seen in all cases)</td>
<td>711±665(47-1544)/499±597(48-1629)</td>
<td>NA</td>
<td>[1]</td>
</tr>
<tr>
<td>16/M</td>
<td>Poor for 6 months</td>
<td>+ (4cm below the RCM)</td>
<td>66/58</td>
<td>Hepatomegaly suggestive of diffuse fatty liver (US)</td>
<td>[2]</td>
</tr>
<tr>
<td>29/F</td>
<td>Poor for 14 years</td>
<td>NA</td>
<td>4300/1500</td>
<td>Hepatomegaly suggestive of diffuse fatty liver (US)</td>
<td>[3]</td>
</tr>
<tr>
<td>13/M,17/F</td>
<td>Poor for several years in both cases</td>
<td>+ (16cm and 15cm below the RCM, respectively)</td>
<td>290/127, 102/147</td>
<td>Hepatomegaly suggestive of diffuse fatty liver (CT and US)</td>
<td>[4]</td>
</tr>
<tr>
<td>33/F</td>
<td>Poor</td>
<td>NA</td>
<td>428/404</td>
<td>Hepatomegaly suggestive of diffuse fatty liver (US)</td>
<td>[5]</td>
</tr>
<tr>
<td>13-70 (32.3±19.5)/M4:F7 (n=11)</td>
<td>Poor for a long time in all cases</td>
<td>+ (seen in 9 out of 11 cases)</td>
<td>211±284(20-940)/308±316(20-910)</td>
<td>NA</td>
<td>[6]</td>
</tr>
<tr>
<td>8/M</td>
<td>Poor for 6 years</td>
<td>+ (6cm below the RCM)</td>
<td>3740/1410</td>
<td>Diffuse hepatomegaly (CT)</td>
<td>[7]</td>
</tr>
<tr>
<td>18/F, 21/M</td>
<td>Poor in both cases</td>
<td>+ (seen in both cases)</td>
<td>NA</td>
<td>Hepatomegaly (CT) and increased echogenic texture of the liver (US)</td>
<td>[8]</td>
</tr>
<tr>
<td>19/F</td>
<td>Poor more than 1.5 years</td>
<td>NA</td>
<td>143/147</td>
<td>No fatty infiltration (US)</td>
<td>[9]</td>
</tr>
<tr>
<td>20/F</td>
<td>Poor for a long time</td>
<td>+</td>
<td>249/383</td>
<td>NA</td>
<td>[10]</td>
</tr>
<tr>
<td>17/F</td>
<td>Poor</td>
<td>+</td>
<td>138/164</td>
<td>Hepatomegaly without steatosis (US)</td>
<td>[11]</td>
</tr>
<tr>
<td>19/F</td>
<td>Poor for a long time and 4 weeks after recovery from DKA</td>
<td>+ (10cm below the RCM)</td>
<td>1228/649</td>
<td>NA</td>
<td>[12]</td>
</tr>
<tr>
<td>27/M</td>
<td>Poor</td>
<td>+</td>
<td>6720/2549</td>
<td>Hepatomegaly of increased density (CT)</td>
<td>[24]</td>
</tr>
<tr>
<td>21/M</td>
<td>New-onset fulminant T1D just after the initiation of insulin treatment</td>
<td>+ (2cm below the RCM)</td>
<td>930/1348</td>
<td>Suggestive of diffuse fatty liver (US), hepatomegaly of decreased density on CT and negative for fatty liver by GR-DE MRI study</td>
<td>Ours</td>
</tr>
</tbody>
</table>

T1D, type 1 diabetes; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GH, glycogenic hepatopathy; Ref, references; RCM, right costal margin; NA, not available; DKA, diabetic ketoacidosis; US, ultrasound; CT, computed tomography; GR-DE, gradient-dual-echo; MRI, magnetic resonance imaging. Age (years) and AST/ALT (IU/L) are represented by mean ± SD.
Takaike et al. described liver dysfunction that was very similar to ours, and, therefore, it is highly possible that many cases with GH could have been inappropriately diagnosed as NAFLD in patients with T1D. The major problem in diagnosing GH is that histological examination is the only reliable tool with which to distinguish GH from NAFLD [1-5], which is the most frequent cause of liver dysfunction seen in diabetes patients [23]. Our report clearly showed that ultrasound was not a useful modality with which to distinguish glycogen accumulation from fat deposition (Fig. 2A, 2B). On the other hand, Sweetser et al. reported the usefulness of CT examination for distinguishing GH from NAFLD; the liver density on CT in patients with GH is increased, whereas it is decreased in patients with fatty liver. Therefore, they claimed that increased liver density in the CT examination would be a clue for the diagnosis of GH (Table 1) [24]. Doppman et al. indeed reported a dose-dependent increase and decrease in CT density as the glycogen content increases and as fat content increases, respectively, by studying artificial specimens [25]. However the liver density observed on CT may not simply increase as in patients with glycogen storage disease [25, 26] because the glycogen deposition in the liver might not be a uniform clinical condition.

In our patient reported herein, CT density was diffusely decreased in the liver when the liver dysfunction was progressing (Figs. 1, 2C), and the MRI study performed a few days after the peak of the liver dysfunction demonstrated that intrahepatic fat accumulation in the liver was highly unlikely (Figs. 1, 3A, 3B). It would
be highly unlikely for fat deposition to be the cause of the low CT density in the liver because fat deposition abundant enough to decrease CT density would not disappear within the short clinical course of the patient described here. Since it was reported that the CT density of the liver decreases and the liver enlarges in the early phase of acute liver failure [27], the decreased liver density observed in our patient seemed to be due to a shock liver. Therefore, these findings suggest to us that a liver CT and/or ultrasound would not be very useful in the diagnosis of GH. In contrast, a gradient-dual-echo MRI sequence was reported to be able to distinguish a fat deposition from an edematous condition, such as acute tissue injury [13, 14], both of which appear as low-density areas on CT. Thus, a gradient-dual-echo MRI sequence could be a clue to diagnose GH by combining with thorough clinical evaluation of the liver dysfunction and hepatomegaly including ultrasound and/or CT examination, without an invasive liver biopsy.

In conclusion, we demonstrated the first case of new-onset fulminant T1D who developed GH just after the initiation of insulin treatment. Our report suggests that GH could have been misdiagnosed as NAFLD in some patients with liver dysfunction accompanied by new-onset T1D. In addition, we showed a potential use of gradient-dual-echo MRI sequence of the liver as a non-invasive and useful tool for diagnosis of GH by distinguishing from NAFLD.

References


