

Glycogenic hepatopathy in children with poorly controlled type 1 diabetes mellitus

Nor Azizah Abu¹, Chooi Bee Lim², and Noor Shafina Mohd Nor^{1,3}

¹Department of Pediatric, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Selangor, Malaysia

²Department of Pediatric, Selayang Hospital, Ministry of Health, Lebuhraya Kepong Selayang, Selangor, Malaysia

³Institute for Pathology, Laboratory and Forensic Medicine (I-PPerForM), Universiti Teknologi MARA (UiTM), Selangor, Malaysia

Abstract. Mauriac syndrome is a rare and underdiagnosed complication of type 1 diabetes mellitus (T1DM). It is characterized by growth retardation, delayed puberty, Cushingoid features, hepatomegaly, and increased transaminase levels. The term glycogenic hepatopathy has been used to describe patients with poorly controlled T1DM and glycogen overload in the hepatocytes but without all the features of Mauriac syndrome. Although rare, glycogenic hepatopathy is reported to be the main cause of hepatomegaly in young patients with T1DM. We report two cases of glycogenic hepatopathy in children with poorly controlled T1DM. Both children had hepatomegaly, elevated liver enzyme levels, and elevated lactate levels. A liver biopsy confirmed the diagnosis of glycogenic hepatopathy in both patients. In conclusion, hepatomegaly with elevated liver enzymes, negative infective and metabolic screenings and persistently elevated plasma lactate levels should raise the suspicion of glycogenic hepatopathy in poorly controlled T1DM. Early diagnosis and improvement in glycemic control are the mainstays of treatment, which can prevent long-term complications.

Key words: Mauriac syndrome, glycogenic hepatopathy, type 1 diabetes mellitus, children

Introduction

Glycogenic hepatopathy or hepatic glycogenosis is a rare complication in patients with poorly controlled type 1 diabetes mellitus (T1DM). It was first described in 1930 by Pierre Mauriac as part of the Mauriac syndrome (MS), which is characterized by growth retardation, delayed puberty, Cushingoid features, hepatomegaly, and increased transaminases (1, 2). In 2006, Torbenson and colleagues proposed the term “Glycogenic Hepatopathy” in patients with poorly controlled T1DM and glycogen overload in the hepatocytes but without all the features of Mauriac Syndrome (3).

Although rare, some reports have suggested that glycogenic hepatopathy is the main cause of hepatomegaly in young patients with T1DM (4). Therefore, it is important to recognize this complication. We report here two cases of glycogenic hepatopathy in children with T1DM.

Case Presentations

Case 1

A 10-yr-old girl with poorly controlled T1DM presented in 2017 with abdominal discomfort and vomiting for 3 d. She was diagnosed with T1DM at the age of 5 yr, and therapy was initiated with multiple daily injections of insulin. She was on sc Glargine 22 u once daily at night (ON) and sc Aspart 8u thrice daily (TDS) (1.38 IU/kg/d). Despite the treatment, she underwent multiple hospitalizations due to diabetic ketoacidosis (DKA), either due to poor compliance or infection. Her HbA1c level was in the range of 12.5–16.1%. She belonged to the poor socioeconomic community, and her mother was a single parent employed as a factory worker. Her elder sister also had T1DM and was on insulin therapy.

On examination, she had no scleral icterus or peripheral signs of chronic liver disease. Her weight was 28.5 kg (10th–25th centile), height was 130 cm (10th centile), and body mass index was 16.8 kg/m² (25th

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Corresponding author: Noor Shafina Mohd Nor, M.D., Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh Campus, Jalan Hospital, 47000 Sungai Buloh, Selangor, Malaysia.

E-mail: drshafina@uitm.edu.my / shafinamohdnor@yahoo.com



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to 50th centile). Her breast was at Tanner stage 2 on pubertal assessment. She had no pubic or axillary hair. Her abdomen was tender in the right hypochondriac region, with hepatomegaly measured 6.5 cm below the costal margin.

Investigations revealed hyperglycemia with no ketoacidosis. Her liver enzymes were elevated with alanine aminotransferase (ALT), 101 IU/l; aspartate aminotransferase (AST), 194 IU/l; and gamma-glutamyl transpeptidase (GGT), 182 IU/l. Other investigations included normal total bilirubin (15.1 μ mol/l), increased serum amylase (517 IU/l) and urine diastase (> 3010 U/l). Her plasma lactate level was elevated at 9.9 mmol/l. Screening for infections, including Hepatitis B surface antigen, Hepatitis C antibody, and HIV antibody, showed negative results. Liver autoantibodies, including anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and anti-liver-kidney microsome antibody (LKM), were also negative. Inborn errors of metabolism (IEM) profiles were normal.

Ultrasound (US) of the abdomen showed an enlarged liver measuring 16.5 cm with normal echogenicity. Liver biopsy revealed diffuse cytoplasmic periodic acid-Schiff staining, with marked accumulation of glycogen within the hepatocytes (**Fig. 1**), which dissolved with diastase treatment, consistent with GH (**Fig. 2**).

She was followed up regularly with an emphasis on the importance of compliance with the diabetic diet and insulin. However, her diabetes was still poorly controlled due to her poor socioeconomic circumstances, with a recent hemoglobin A1c (HbA1c) level of 12%. She showed deterioration in her growth parameters with a weight of 33.3 kg at the age of 13 yr (on the 3rd centile) and height 136 cm (less than 3rd centile). Her pubertal stage was Tanner stage 4. The liver was enlarged 7 cm below the costal margin. Her AST level was still slightly increased at 40 IU/l.

Case 2

A 10-yr-old boy with underlying T1DM since the age of 4 yr and on sc multiple daily injections of insulin therapy, sc Glargine 4u ON, and sc Aspart 4u TDS (0.7 u/kg/d) was admitted in 2017 due to generalized body swelling for 4 d. There was no frothy urine, hematuria, or oliguria. The patient did not have any cardiac symptoms. He had three previous hospital admissions: hypoglycemic seizure on one occasion and DKA on two occasions. Blood sugar monitoring at home showed fluctuating blood sugar levels, ranging from low to high. His HbA1c level ranged from 10 to 13.3%.

On examination, he had no jaundice and had no peripheral signs of chronic liver disease. His weight was 23 kg (less than 3rd percentile), height 128 cm (less than 3rd centile), and body mass index 14.04 kg/m² (less than 3rd percentile). The liver was palpable 5 cm below the costal margin. He had ascites and scrotal and lower limb edema. Other findings on systemic examination were unremarkable.

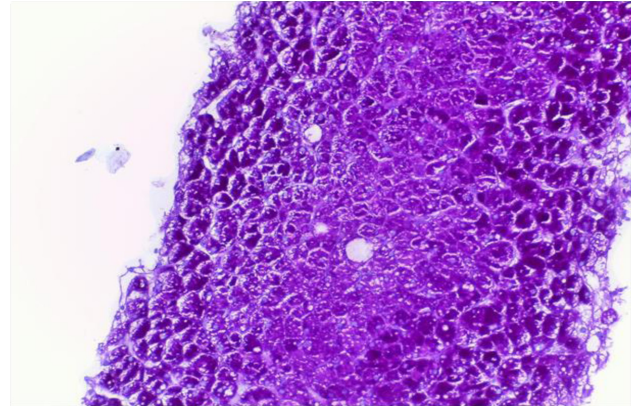


Fig. 1. Histology from the liver biopsy of Case 1 showing diffuse cytoplasmic periodic acid-Schiff stain, indicating a marked accumulation of glycogen content within the hepatocytes.

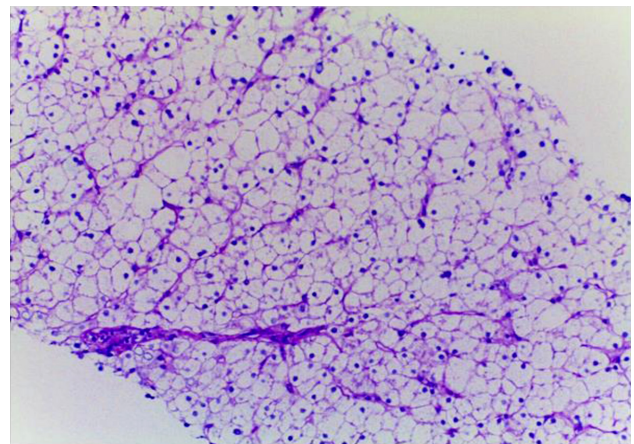


Fig. 2. Histology from the liver biopsy of Case 1 showing periodic acid-Schiff stain of hepatocytes dissolved with diastase treatment, indicating glycogen deposition in the liver.

In the emergency department, his blood sugar level was found to be low. Investigations to rule out renal and cardiac causes of edema were normal. However, his liver enzymes were not normal, with an ALT level of 286 IU/l, AST level of 128 IU/l, and GGT level of 187 IU/l. Serum albumin was 37 g/l, and bilirubin was 6 μ mol/l. Serum lactate was increased at 6.88 mmol/l. Levels of serum copper, ceruloplasmin, alpha-1 antitrypsin, and alpha-fetoprotein were normal. The infective and autoimmune screening tests showed negative results.

Liver US showed hepatomegaly measuring 15.7 cm with normal liver parenchymal echogenicity. Doppler US of the lower limbs was normal. Liver biopsy showed changes similar to those in the first case, consistent with glycogenic hepatopathy. Follow-up was continued at the pediatric endocrine clinic. There were significant psychological concerns; hence, he was referred to a psychologist for counseling. He had better diabetic control with a recent HbA1c level of 9% at the age of 13

yr. His weight and height parameters also improved to the 3rd percentile. His hepatomegaly resolved, and the liver enzyme levels normalized.

Discussion

Glycogenic hepatopathy develops due to excessive accumulation of glycogen in the hepatocytes, leading to hepatomegaly and liver impairment (2, 5). In the presence of hyperglycemia, glucose enters hepatocytes by facilitated diffusion. It is then irreversibly phosphorylated by the enzyme glucokinase to glucose-6-phosphate and subsequently converted to glycogen under the action of insulin (6). Therefore, a history of poorly controlled diabetes, elevated liver enzymes, and characteristic histological changes on liver biopsy are diagnostic of glycogenic hepatopathy (7, 8).

Both of our patients had elevated lactate levels. Similar findings were reported by other authors who reported glycogenic hepatopathy (9–14). However, the underlying mechanism remains unclear. One hypothesis suggests that liver injury due to glycogen accumulation causes impaired gluconeogenesis; hence, the metabolism of pyruvate is shifted to lactate instead of glucose. Insulin administration further inhibits gluconeogenesis and increases the lactate levels. Another hypothesis is that enhanced glycolysis in the splanchnic region causes elevated lactate levels in chronic liver disease (13, 14).

Both these patients had completely different clinical courses of glycogenic hepatopathy. The diabetic control in our first patient remained poor for the past 3 yr, and she continued to have hepatomegaly along with mild derangement abnormalities in her liver enzymes, in addition to worsening growth parameters. In contrast, our second patient showed improvement in his sugar control, which was followed by a resolution of his hepatomegaly and liver enzyme elevation, as well as improvement in his growth. This is consistent with the findings of many studies that reported remission of clinical and laboratory abnormalities in patients with glycogenic hepatopathy with optimization of glucose control (15–23). The negative effects of poor metabolic control on weight and height were observed in both patients. These are in keeping with previous reports that documented negative correlations between HbA1c levels and growth indices (24–27). This highlights the importance of good glycemic control in every patient with T1DM to reduce the risk of complications.

In recent times, MS in children has become less common, particularly with the availability of new insulin analogs with intensive insulin therapy. Nevertheless, some emerging case reports describing glycogenic hepatopathy in T1DM patients without other features

of MS have shown that this rare complication of T1DM must be acknowledged (28). Our cases showed similar challenges in diabetic care, with both having poor glycemic control due to unfortunate socioeconomic background and psychological challenges. These render them at a high risk of complications with recurrence of DKA. Some previously reported cases of glycogenic hepatopathy also had similar socioeconomic challenges, which led to poor glycemic control (29).

One of the most important differential diagnoses in our cases was non-alcoholic fatty liver disease (NAFLD), which is associated with obesity and is more commonly found in patients with type 2 diabetes mellitus. Up to 19.3% of patients with T1DM have biopsy-proven NAFLD (30). It is difficult to distinguish between glycogenic hepatopathy and NAFLD clinically as both can cause hepatomegaly, elevation in liver enzymes, and increased echogenicity on US (31). However, gradient dual-echo magnetic resonance imaging can help differentiate between glycogenic hepatopathy and NAFLD. T1-weighted images in NAFLD showed increased intensity during the in-phase compared to the opposed-phase, whereas the intensities were similar in both phases in glycogenic hepatopathy (32, 33). The final diagnosis is based on liver biopsy. The prognoses of the two conditions differed significantly. As mentioned above, glycogenic hepatopathy has a more benign clinical course with a potential for complete clinical and biochemical resolution once optimal glycemic control is achieved (22). Nevertheless, between 20% and 30% of patients with NAFLD progress to non-alcoholic steatohepatitis (NASH), with the consequent risk of cirrhosis and liver cancer (34).

Conclusion

Hepatomegaly with elevated liver enzymes, negative infective and metabolic screening, and persistently elevated plasma lactate levels should raise the suspicion of glycogenic hepatopathy in patients with poorly controlled T1DM. Early diagnosis and improvement in glycemic control are the mainstays of treatment, which can prevent long-term complications.

Conflict of interests: The authors declare no conflicts of interest.

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