Glycogenic Hepatopathy: A Rare Complication of a Common Disease

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Abstract

Glycogen hepatopathy is a rare complication seen mainly in patients with diabetes mellitus whom having a poor glycemic control. We report an 11-year-old female with type 1 Diabetes Mellitus and autoimmune hypothyroidism presenting with transaminitis and hepatomegaly, secondary poor glycemic profile. After excluding the common causes of hepatitis, a liver biopsy performed to rule out autoimmune hepatitis or congenital hepatic fibrosis in view of positive family history. Liver histology showed typical features of glycogen hepatopathy. Intense management of diabetes with improvement of the glycemic control resulted in normalization of liver transaminases and regression of hepatomegaly in a 6–month period. This case highlights the importance of considering glycogen hepatopathy as one of the differential diagnosis of hepatitis in type 1 diabetes mellitus patients. Glycogen hepatopathy has a good prognosis when achieving good glycemic control.

Keywords: Glycogen Hepatopathy; Diabetes Mellitus Type One; Transaminases; Hepatomegal.

Introduction

Type one diabetes mellitus (DM) is the most common chronic pediatric endocrine metabolic disease with gradually increasing incidence.[1] Poorly controlled diabetes can lead to macro and microvascular complications. Nevertheless, the impact can also extend to some tissues such as the liver. Glycogen hepatopathy is one of the rare and under-recognized complications seen in patients with poorly controlled diabetes.[2] It is characterized by excessive accumulation of glycogen in hepatocytes, resulting in hepatomegaly, and transaminitis with or without liver dysfunction.[2,3] The clinical presentation can mimic non-alcoholic fatty liver disease (NAFLD) as both condition can present with abdominal pain or with an incidental findings of elevated transaminases . It is essential to differentiate between GH and NAFLD. The only way to make a definitive diagnosis is by liver biopsy. GH results due to hyperglycemia which leads to excessive glycogen storage due to high levels of insulin. However, it has good prognosis as it can be completely reversed with good glycemic control.[4]

Case Report

An 11-year-old female with poorly controlled T1DM, presented with elevated liver enzymes, during an elective admission for hyperglycemia management. At that time, she had no history of fever, cough, abdominal pain, or

vomiting. She had normal urinary and bowel habits. She was diagnosed with T1DM at age of 5 years, followed by autoimmune hypothyroidism at age of 10 years. She wass on multiple daily insulin injections (MDI) regimen, and levothyroxine. Her parents are related as first cousin and both have hypothyroidism on levothyroxine. Her paternal cousin diagnosed with congenital hepatic fibrosis. Since the diagnosis of T1DM, they patient had issues with adherence to insulin and age-appropriate dieting. Physical examination revealed a thin-build girl with height at 9th centile, weight and BMI < 3rd centile. She was pale but not icteric. She had no stigmata of chronic liver disease. Abdominal examination revealed a soft, non-tender liver 5 cm below the right costal margin. Laboratory tests were significant for high glycosylated hemoglobin (HbA1c) and transaminitis (Table1). Abdominal ultrasonography showed enlarged liver of 18.3 cm with diffuse increased echogenicity of diffuse fatty infiltration. She tested negative for viral hepatitis, Wilson disease and autoimmune hepatitis. Liver biopsy showed preserved lobular architecture with unremarkable portal tracts. The sinusoids appeared compressed by the enlarged hepatocytes, which exhibit pale cytoplasm, glycogenated nuclei and prominent cell borders. The periodic acid–Schiff (PAS) stain highlights the intracytoplasmic glycogen. There was no steatosis, cholestasis, necrosis, or fibrosis. No stainable iron was present. Periodic acid Schiff plus diastase (PAS/D) stain was negative for alpha 1- antitrypsin globules. [Figure1].

Table 1: The blood investigations done for the patient at the time of evaluation for elevated transaminases.

Test	Value	Reference Range
Glycosylated hemoglobin (HbA1c)	11.9%	4.7-5.7%
Alanine transaminase (ALT)	801 U/L	0-33 U/L
Aspartate aminotransferase (AST)	3080 U/L	0-32U/L
Alkaline phosphatase (ALP)	222 U/L	129-417 U/L
Total bilirubin	5 umol/L	0-17 umol/L
Albumin	40 g/L	38-54g/L
Total protein	63g/L	60-80 g/L
Gamma-glutamyl transferase (GGT)	148 U/L	<31 U/L
Anion gap	24 mmol/l	5-13mmol/l
Bicarbonate	15mmol/l	22-29mmol/l
Sodium	132 mmol/l	135-145mmol/l
Potassium	4.3 mmol/l	3.5-5.1 mmol/l
Creatinine	39umol/l	29-56 umol/l
Urea	3.7 mmol/l	2.8-8.1 mmol/l
Hemoglobin level was	10.9g/dl	11.5-15.5 g/dl
Prothrombin Time (PT)	10.1 sec	9.9-11.5 sec
International normalized ratio (INR)	0.94	0.9-1.10
Free Thyroxine (T4)	13.4 pmol/l	12.5-21.5 pmol/l
Thyroid- stimulating hormone (TSH)	15.73mIU/L	0.6-4.84 mIU/L

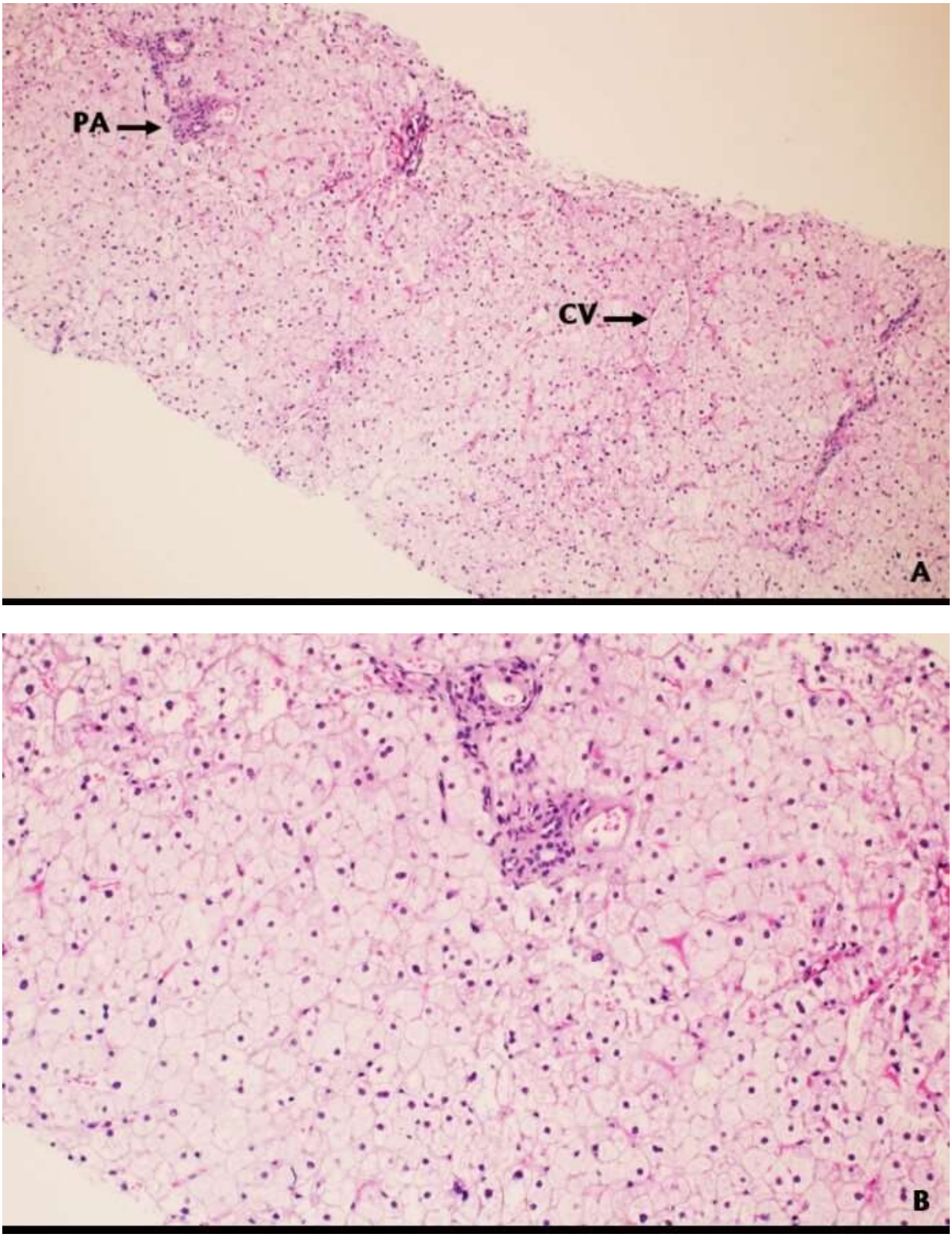

Figure 1: (a) The liver displays intact lobular architecture, Hematoxylin and Eosin stain x 10. PA: Portal Area; CV: Central Vein. **(b)** The hepatocytes show rarefied, pale-staining cytoplasm and prominent cell borders contrasting with

the pale cytoplasm. The sinusoids are compressed. There is no steatosis, cholestasis, necrosis, or fibrosis. The change involves the entire lobule. There is no portal inflammation or duct injury. H/E x 20. **(c)** The cytoplasm stains intensely with periodic acid–Schiff (PAS) and this staining disappears completely after diastase digestion x 20.

After confirming the diagnosis of glycogen hepatopathy, patient's management was intensified again. Serial follow-up visits showed declining levels of transaminases which normalized after six months. Her HbA1c remained to be high, ranging from 9.4 to 14.2%. The patient continued to have major issues with adherence to diet and insulin. She continued resisting to move ahead with carbohydrate counting, and missing her medications. Her liver enzymes noted to be fluctuating, depending on the glycemic control at the time.

Discussion

Glycogen hepatopathy (GH) is under-recognized complication in poorly controlled diabetic patients.[2]The exact reason why it develops in a subset of patients with T1DM is not fully understood. It was first noted when short-acting insulin was introduced to control DM in patients with poorly controlled T1DM,[5] and it is believed to be associated with asynchronous fluctuating levels of blood glucose and insulin.[6] High levels of blood glucose can lead to glucose accumulation in the hepatocytes by passive diffusion. It is then converted into glucose-6-phosphate (G-6-P) by hepatic glucokinase, which is subsequently converted to glycogen by the action of glycogen synthase enzyme.[6,7]

The presence of insulin is required for the activation of glycogen synthase by dephosphorylation. In a patient with poorly controlled T1DM, constant high blood glucose levels mean higher levels of G-6-P within the hepatocytes.[5,7] A sudden rise in serum insulin converts G-6-P into glycogen. The net result of this glucose-insulin imbalance is accumulation of glycogen within the hepatocytes and inhibition of further glycogenolysis.[6,8] Therefore, this becomes more evident in patients who are not taking their insulin doses regularly and especially when they do often miss their long-acting insulin on the MDI regimen.

GH has also been reported in T2DM, administration of short-term high-dose steroid and in dumping syndrome[2'3]. The clinical presentation varies from signs and symptoms of diabetic ketoacidosis, or acute hepatitis with abdominal pain, nausea, and vomiting to asymptomatic incidental finding of elevated liver enzymes. Physical examination usually reveals hepatomegaly which might be tender. Ascites is less common but it has been reported.[3] Laboratory work up usually shows elevation of liver enzymes however synthetic liver function is usually preserved.[2,3]

It is very important to distinguish between NAFLD and GH. NAFLD can progress to advanced liver disease, cirrhosis and or hepatocellular carcinoma whereas, GH is a more benign, reversible condition with good prognosis when the patient manages to achieve a good glycemic control. Table 2 provides comparison between the two clinical entities.

Table 2: Comparison between glycogenic hepatopathy and non-alcoholic fatty liver disease.

	Glycogenic Hepatopathy (GH)	**Non-alcoholic Fatty Liver Disease (NAFLD)**
Definition	Excessive glycogen accumulation in the liver occurs as a result of poorly controlled diabetes, especially in type 1 diabetes	Spectrum of liver conditions characterized by the accumulation of fat in liver not related to alcohol consumption
Causes	Primarily associated with poorly controlled type 1 diabetes	Strongly associated with obesity, insulin resistance, type 2 diabetes, and metabolic syndrome. Can also result from factors such as genetic predisposition, medications, or other conditions
Pathophysiology	Hyperglycemia leads to excessive glycogen storage due to high levels of insulin or insulin-like effects	Increased fat accumulation in hepatocytes. It may progress from simple steatosis to non-alcoholic steatohepatitis (NASH), which can cause fibrosis.
Symptoms	Often asymptomatic but may present with hepatomegaly or abdominal discomfort	Often asymptomatic but may present with hepatomegaly or abdominal discomfort

Radiological Imaging	**Heterogeneous Liver Appearance** heterogeneity can result from variable glycogen distribution **Ultrasound Findings:** Hyperechoic Liver due to glycogen, less pronounced compared to fat accumulation	**Heterogeneous Liver Appearance** heterogeneity is typically due to varying degrees of fat deposition **Ultrasound Findings:** Hyperechoic Liver due to fat infiltration
Liver Biopsy	**Glycogen Accumulation:** Hepatocytes show diffuse and prominent glycogen deposition, detectable with special stains like Periodic Acid-Schiff (PAS). **Normal Liver Architecture:** DGH usually lacks significant inflammation, steatosis, or fibrosis unless there is prolonged liver damage. **Hepatocyte Swelling:** Cells may be swollen from excess glycogen but show less ballooning or necrosis compared to non-alcoholic steatohepatitis (NASH) **Fibrosis:** Not a prominent feature unless there has been extended liver injury or secondary complications	**Steatosis**: Fat accumulates in hepatocytes as microvesicular or macrovesicular droplets, often diffusely throughout the liver. **Inflammation**: Advanced stages like NASH show inflammation with cells such as lymphocytes and neutrophils. **Ballooning Degeneration**: Hepatocytes may be swollen and degenerated, a hallmark of NASH. **Fibrosis**: In severe cases, fibrosis can develop, starting as perisinusoidal or portal fibrosis and potentially progressing to bridging fibrosis or cirrhosis.
Treatment	Managing blood sugar levels effectively usually leads to improvement or resolution of the condition	Lifestyle changes (weight loss, diet, exercise), management of underlying conditions (e.g., diabetes), and sometimes medications

The gold standard test to diagnose GH is liver biopsy. Histology examination is straightforward and typically shows ballooning of the hepatocytes with clear cytoplasm and well-defined cell border. The PAS stain highlights the accumulation of glycogen within the cytoplasm. The architecture is usually preserved with no inflammation or necrosis.[7,8]

Improving glycemic control is the mainstay of the management of GH. It results in complete clinical and biochemical improvement and normalization of the affected values. It is reported that symptoms can be reversed in 2 to 14 weeks with a strict glycemic control. Our patient took 24 weeks to normalize her liver enzymes which is most likely due to fluctuating adherence to her carbohydrate counting and taking the appropriate dose of insulin. GH could recur and relapse with poor glycemic control, therefore it is essential to follow these patients up for any relapse of symptoms if persistent control of hyperglycemic is not achieved.[5] Our patient was referred to child and adolescent mental health services for further support.

Conclusion

GH is one of the differential diagnoses in T1DM with hepatomegaly and elevated liver enzymes. It is caused by a reversible accumulation of excess glycogen in hepatocytes. Liver biopsy is the gold standard to diagnose and differentiate it from NAFLD which carries a different prognosis. Although it is a rare complication, but it is extremely important to be aware of this condition to prevent delay or misdiagnosis this condition. GH may recur and worsen with poor glycemic control, making it essential to closely monitor patients for symptom relapse if stable blood sugar levels are not maintained. Therefore, multidisciplinary management, including psychological support for both patients and their families, is crucial in managing chronic conditions like this.

Further data and studies are needed to better understand the pathophysiology, risk factors, prognosis, and risk of liver fibrosis to come up with a non-invasive, rapid diagnostic test to avoid the extensive work-up and associated costs in evaluating suspected cases of GH.[5]

Disclosure

The authors declared no conflicts of interest. Informed consent was obtained from the patient's father.

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