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Single Case

Glycogen Hepatopathy: A Rare and Underrecognized Cause of Recurrent Transaminitis in Patients with Uncontrolled Type 2 Diabetes Mellitus

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Keywords

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Abstract

Glycogen hepatopathy (GH), characterized by reversible transaminitis and hepatomegaly, results from excessive accumulation of glycogen in hepatocytes. GH has been well described in the literature as a rare cause of transaminitis in children and young patients with uncontrolled type 1 diabetes mellitus and has rarely been reported in type 2 diabetic patients. Hyperglycemia and hyperinsulinemia are believed to be a metabolic substrate for hepatic glycogen accumulation and in order to cause glycogen hepatotoxicity. We present the case of a 54-year-old woman with poorly controlled insulin-dependent type 2 diabetes who was hospitalized twice within 1 month with diabetic ketoacidosis/hyperosmolar hyperglycemic state and reversible transaminitis. Interestingly, she had normal liver function tests performed at the time of admission and transaminitis was noted 1 day later, after she was treated with high doses of intravenous insulin therapy. Subsequently, liver enzymes recovered to normal levels with optimization of glucose control.

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Introduction

Glycogen hepatopathy (GH), characterized by reversible transaminitis and hepatomegaly, results from excessive accumulation of glycogen in hepatocytes. Mauriac [1] first defined GH in a child with brittle diabetes, as a component of Mauriac syndrome, characterized by delayed development, hepatomegaly, cushingoid appearance, and delayed puberty. GH has been well described as a rare cause of transaminitis in young patients with uncontrolled type 1 diabetes mellitus and has rarely been reported in type 2 diabetic patients. Hyperglycemia and hyperinsulinemia are believed to be a metabolic substrate for hepatic glycogen accumulation and in order to cause glycogen hepatotoxicity. Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease for both the general and the diabetic populations currently due to its association with obesity and metabolic syndrome. Clinician awareness of GH should prevent diagnostic delay and will provide better insight into the prevalence of GH. In addition, the distinction between GH and NAFLD is important, as prognosis of both diseases may be different [1, 2].

Case Presentation

A 54-year-old Hispanic woman presented to our emergency room with complaints of abdominal pain and nausea for 2 days. The patient denied fever, vomiting, diarrhea, yellow discoloration, sick contact, recent traveling, Tylenol ingestion, and she denied a history of herbal medication use. Her medical history was significant for diabetes mellitus type 2, asthma, depression, chronic back pain, and laparoscopic cholecystectomy. Her medications included insulin aspart 30 units 3 times daily with meals, insulin Lantus 35 units at bedtime, aspirin 81 mg once daily, albuterol inhaler as needed, fluticasone/salmeterol twice daily, and clonazepam daily. She had no family history of diabetes mellitus or liver disease. She reported cigarette smoking and denied alcohol and drug use. On presentation, her temperature was 97.9° F, blood pressure 143/92 mm Hg, pulse 97 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 98% on room air, and her BMI was 24. Physical exam was unremarkable except for mild hepatomegaly. Initial laboratory investigations were consistent with a hyperosmolar hyperglycemic state with normal liver enzyme levels, and she was started on intravenous insulin therapy along with aggressive fluid resuscitation. On the second day of hospitalization, she was noted to have elevated liver enzyme levels with aspartate transaminase/alanine aminotransferase (AST/ALT) of 424/145 U/L and alkaline phosphatase (ALP) of 187 U/L (Table 1). However, liver enzymes improved on day 4, with optimization of her blood sugar levels and substitution of intravenous insulin with subcutaneous insulin.

Three weeks prior to this admission, she was admitted to the hospital with diabetic ketoacidosis and normal liver function tests at the time of admission. One day after starting intravenous insulin, she developed transaminitis with AST of 665 U/L and ALT of 231 U/L that also resolved to normal values with optimization of blood sugar levels and upon transition from intravenous insulin to subcutaneous insulin. Hepatitis workup, including viral hepatitis A, B, C, iron profile, anti-neutrophil antibody, anti-mitochondrial antibody, celiac panel, serum ceruloplasmin, anti-smooth muscle antibody, and anti-liver kidney muscle antibody, was

unremarkable (Table 2). Ultrasound of the abdomen showed hepatomegaly with normal liver contour and echo pattern. Subsequent magnetic resonance pancreatography revealed no biliary tree pathology.

Ischemic hepatopathy can cause acute appearance and rapid amelioration of liver enzymes; however, there was no episode of hypotension during both hospitalizations. Moreover, temporal relationship with insulin therapy in the setting of hyperglycemia was more suggestive of a diagnosis of GH. Similarly, NAFLD was considered an alternative cause of transaminitis due to her history of diabetes, dyslipidemia, and obesity. However, NAFLD rarely causes aminotransferase elevation similar to the one observed in this patient. The acute increase in transaminases immediately after starting insulin therapy and rapid normalization of liver enzymes is uncommon in NAFLD. Nonetheless, the presence of some degree of underlying fatty infiltration could not be ignored in this case [5]. Other common and possible etiologies which could have contributed to transaminitis include alcoholic liver disease, drug-induced liver injury, and severe sepsis and were excluded due to the absence of alcohol use, known hepatotoxic drug, and underlying sepsis, respectively. A liver biopsy is a definitive way to diagnose GH, but the patient did not agree to the procedure.

Discussion

Transaminitis is a very common laboratory abnormality in patients with diabetes mellitus, obesity, and metabolic syndrome. The prevalence of elevated ALT level is 9.5% among type 1 and 12.1% among type 2 diabetics. These percentages are higher than those expected in the general population (2.7%). NAFLD is currently the most common cause of chronic liver disease for both the general and the diabetic populations due to its association with obesity and metabolic syndrome. Therefore, NAFLD was observed more frequently in type 2 diabetes cases compared to type 1 diabetes. However, it should be noted that NAFLD is a diagnosis of exclusion [1].

GH, a disease that develops due to excessive hepatic glycogen accumulation, is characterized by hepatomegaly and elevated liver enzyme levels. GH was first described in 1930, as a component of Mauriac syndrome, which includes type 1 diabetes, delayed development, hepatomegaly, cushingoid appearance, and delayed puberty [1]. However, it can also be observed in type 1 diabetic individuals without the other components of Mauriac syndrome. Biochemically, the glycogen accumulation takes place when hyperglycemia activates glycogen synthase enzyme by inhibiting glycogenolysis via glycogen phosphorylation inactivation. Inside the cell, glucose is converted into glucose-6-phosphate and ultimately to glycogen by enzyme glycogen synthase. The enzyme glycogen synthase is converted from an inactive (phosphorylated) form into the active (dephosphorylated) form by a phosphatase. The phosphatase concentration is maintained by insulin and relies on the presence of glucose [3–5]. Hepatic glycogen levels are regulated by balance between glycogenesis and glycogenolysis. The entry of glucose into hepatocytes is due to passive diffusion independent of insulin levels. Therefore, frequent hyperglycemic episodes followed by excessive insulin use in order to optimize the glucose level are believed to be the primary pathogenic mechanism of hepatomegaly and transaminitis in poorly controlled diabetic patients. Accumulation of glycogen in the liver occurs when high insulin levels activate glycogen synthase, which further accelerates the

biochemical process of glycogen deposition. Liver biopsy is mandatory for the diagnosis of GH and NAFLD. Persistent and relatively mild disturbance in liver function favors NAFLD; transaminase flares are more compatible with GH.

The hallmark of GH is its reversibility with improved glycemic control, unlike hepatic steatosis; glycogen overload is not known to progress to fibrosis, distinct from fatty liver disease [4]. In addition, ultrasound findings are not helpful in distinguishing NAFLD from GH because both fatty liver and glycogen overload could show a similar ultrasound finding as mild hyperechoic hepatic parenchyma. Consequently, the condition is often misdiagnosed, and it results in wasting medical resources. A final distinction can be made with a liver biopsy. In general, GH is characterized by several histological features which include (1) marked glycogen accumulation. After conventional tissue preparation (fixation by formaldehyde solution and staining with hematoxylin and eosin), the glycogen is usually removed from the hepatocytes. Thus, the hepatocytes are diffusely swollen with a pale cytoplasm and accentuation of the cell membranes, frequently with displacement of the nuclei to the cell periphery, the sinusoids are compressed by swollen hepatocytes, and glycogenated nuclei and giant mitochondria are present; glycogen accumulation within hepatocytes is demonstrated by periodic acid-Schiff staining which disappeared after digestion with diastase; (2) no or a minimal change in fat content; (3) the absence of or minimal inflammation; (4) the absence or minimal presence of spotty lobular necrosis; and (5) intact liver architecture without or with minimal fibrosis [5]. Although GH is definitively diagnosed histologically, a gradient dual-echo magnetic resonance imaging sequence combined with computed tomography of the liver is a powerful methodology for distinguishing GH from NAFLD [5]. The correct diagnosis of this disease is important given its potential resolution after improved glycemic control. It is essential to differentiate GH from other liver disorders, including NAFLD, to avoid unnecessary workup, prevent diagnostic delay, and provide high-value care.

Conclusion

Based on concomitant elevation of transaminases with hyperglycemia and temporal association with insulin therapy, it is reasonable to conclude that this intermittent transaminase elevation is secondary to GH. Nonetheless, GH cannot be confirmed clinically or by ultrasound alone and it always requires liver biopsy for a definitive diagnosis. The reversibility of transaminase elevations in this patient indicates a more benign course of GH. Clinician awareness of GH should prevent diagnostic delay and will provide better insight into the prevalence of GH. In addition, the distinction between GH and NAFLD is important, as the prognosis of both diseases may be different. GH has been known to have a benign nature, whereas NAFLD could progress into advanced liver disease such as cirrhosis or hepatocellular carcinoma [2]. This case highlights this underdiagnosed entity in type 2 diabetics with acute relapsing hepatitis, hence prompting the clinician to consider this condition in the differential diagnosis as one of the possible etiologies of reversible liver injury.

Statement of Ethics

Ethics approval: not obtained.

Consent for publication: consent obtained.

Patient's confidentiality is maintained.

Disclosure Statement

The authors declare that they have no competing interests. This case has never been published before and the authors have no conflict of interest.

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Author Contributions

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Table 1. Biochemical testing at second admission

	Day 1	Day 2	Day 4	After discharge
Serum glucose, mg/dL	808	104	98	275
Anion gap, mmol/L	15	12	14	17
Lactic acid, mmol/L	1.1	0.9		
Bicarbonate, mEq/L	23	24	24	26
Sodium, mEq/L	122	138	142	139
Potassium, mEq/L	4.1	3.4	3.6	3.4
Serum ketone (qualitative)	+++			
Alanine aminotransferase, U/L	15	145	69	14
Aspartate transaminase, U/L	10	424	33	13
Alkaline phosphatase, U/L	186	187	147	186
Total bilirubin, mg/dL	0.3	0.2	0.2	0.4
Ethanol, mg/dL	<10			

Table 2. Laboratory evaluation showing workup done during the first admission to evaluate the cause of abnormal liver function tests

	Day 1	Day 2	Discharge
Serum glucose, mg/dL	779	157	140
Anion gap, mmol/L	23	9	10
Lactic acid, mmol/L	1.4	0.9	1.1
Serum bicarbonate, mEq/L	18	25	23
Sodium, mEq/L	125	135	139
Potassium, mEq/L	4.7	3.0	4.0
HbA _{1c} , %	22.6		
Alanine aminotransferase, U/L	24	231	15
Aspartate transaminase, U/L	16	665	10
Alkaline phosphatase, U/L	187	162	186
Total bilirubin, mg/dL	0.3	0.3	0.3
Hepatitis A IgG	Positive		
Hepatitis A IgM	Negative		
Hepatitis B surface antigen	Negative		
Hepatitis B surface antibody	Positive		
Ethanol, mg/dL	<10		
Anti-hepatitis C antibody	Negative		
Ferritin, ng/mL		194	
Anti-neutrophil antibody	Negative		
Anti-mitochondrial antibody	Negative		
Serum acetone (qualitative)	Positive		
Serum ceruloplasmin, mg/dL	26		
HIV	Negative		
Anti-smooth muscle antibody	Negative		
Liver kidney microsomal assay ≤20	Negative		