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GLYCOGENIC HEPATOPATHY: A COMPLICATION OF UNCONTROLLED DIABETES

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Abstract

Objective—To describe a case of hepatomegaly and elevated transaminases in a patient with glycogenic hepatopathy (GH) as a complication of uncontrolled diabetes.

Methods—Clinical, laboratory, and pathological information are described.

Results—An 18-year-old male with uncontrolled type 1 diabetes and recurrent diabetic ketoacidosis (DKA) presented with abdominal distention and severe hyperglycemia. Physical examination revealed massive hepatomegaly. Laboratory evaluation showed anion-gap metabolic acidosis, ketonuria, and markedly elevated aspartate and alanine amino transaminases (AST = 1,162 IU/L and ALT = 598 IU/L, respectively). Despite resolution of DKA with insulin infusion, transaminases continued to increase (peak AST = 3,725 U/L, ALT = 1,049 U/L) with no signs of liver failure (normal coagulation profile and albumin level). Abdominal ultrasonography revealed an enlarged liver with moderate echogenicity, consistent with steatosis. Extensive evaluation for causes of hepatitis including toxic, autoimmune, genetic, and infectious diseases was unrevealing. Liver biopsy showed no signs of nonalcoholic fatty liver disease (NAFLD), such as fibrosis, steatosis, or portal inflammation. However, swollen hepatocytes with glycogen accumulation consistent with GH were seen.

Conclusion—GH can present as hepatomegaly and elevated liver transaminases in patients with uncontrolled diabetes. Clinicians should consider GH in patients with uncontrolled diabetes after ruling out other common causes. Liver ultrasound cannot differentiate this condition from the

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

more commonly seen NAFLD. Although liver biopsy remains a gold standard, evaluation with magnetic resonance imaging may be considered as a less invasive alternative in the appropriate clinical setting.

INTRODUCTION

Glycogenic hepatopathy (GH) is the hallmark pathological finding of Mauriac syndrome, first described in 1930 in children with uncontrolled type 1 diabetes, delayed growth, cushingoid features, hypercholesterolemia, hepatomegaly, and elevated liver transaminases (1). More recently, it has been recognized that adolescents and adults with uncontrolled diabetes on insulin therapy may present with hepatomegaly and elevated transaminases without the other classic syndromic features (2). A recent small case series also identified an elevated level of lactic acid as part of the syndrome (3). GH has been traditionally diagnosed by liver biopsy; however, less invasive alternatives, such as gradient-dual-echo magnetic resonance imaging (MRI), have been recently suggested (4).

Here we present a young male with poorly controlled diabetes presenting with hepatomegaly, elevated transaminases, lactic acidosis, and liver histopathology findings consistent with GH. Since GH is probably underrecognized due to similarities with nonalcoholic fatty liver disease and the need for liver biopsy to establish a definitive diagnosis (5), we also propose an algorithm to assist clinicians with the diagnosis.

CASE REPORT

An 18-year-old Hispanic male with uncontrolled type 1 diabetes and recurrent diabetic ketoacidosis (DKA) presented to the emergency department complaining of abdominal pain and distention for weeks, worsening over the last few days. He also endorsed nausea, early satiety, and bloating. He reported normal growth and pubertal development. He has had multiple hospitalizations for DKA due to poor compliance with insulin therapy. On presentation, he was tachycardic, with normal blood pressure, respiratory rate, oxygen saturation, and temperature. On general examination, he had a thin body constitution with no acanthosis nigricans. No syndromic features were noted. He had dry mucous membranes and a nontender but massive hepatomegaly.

Initial laboratory evaluation showed severe DKA (glucose of 1,166 mg/dL, anion gap of 22, and ketonuria) and elevated liver transaminases. Notably, lactic acid was also elevated at 2.4 mmol/L on presentation and peaked at 8.0 mmol/L on day 2 of hospitalization. DKA was managed in the intensive care unit with continuous intravenous regular insulin infusion, and the patient was subsequently transitioned to the medicine floor on a basal-bolus subcutaneous insulin regimen. As seen in Figure 1, despite the resolution of DKA with insulin therapy, liver transaminases continued to increase from baseline (aspartate transaminase [AST] = 1,162 IU/L and alanine transaminase [ALT] = 598 IU/L), peaking on day 3 (AST = 3,725 U/L and ALT = 1,049 U/L). However, no signs of acute liver failure were observed; bilirubin, albumin level, and coagulation profile remained normal during his hospitalization. Abdominal ultrasonography revealed an enlarged liver (25 cm) with moderate echogenicity, suggestive of steatosis.

Given the degree and progressive elevation of liver transaminases, which were not consistent with hepatic steatosis, an extensive evaluation for other causes of hepatomegaly and hepatitis was pursued. Evaluation for toxins, autoimmune, genetic, and infectious etiologies were unrevealing. An ultrasound-guided liver biopsy was performed and showed swollen hepatocytes with intracytoplasmic glycogen accumulation that was highlighted with periodic acid–Schiff (PAS) staining (Fig. 2), consistent with GH. As glycemic control improved, liver transaminases started to decrease on day 4 (Fig. 1) and abdominal symptoms mostly resolved. He was discharged home with close outpatient follow-up.

DISCUSSION

We described a case of hepatomegaly and elevated liver transaminases in a patient with poorly controlled type 1 diabetes. Based on the clinical presentation and liver biopsy results, we concluded that GH was the final diagnosis. As seen in this case, it has been recognized that adolescents and adults with uncontrolled diabetes on insulin therapy may present with hepatomegaly and elevated transaminases without the other classic features of Mauriac syndrome such as delayed growth and cushingoid features (2). Although the true incidence of GH is unknown, van den Brand et al (6) found a total of 42 patients from 14 case reports or case series that were published from 1990 to 2009. The authors noticed that up to 95% of these patients had type 1 diabetes.

Unlike most organs where insulin facilitates glucose entry to cells, excess glucose enters hepatocytes by insulin-independent passive diffusion. Concomitant presence of insulin activates glycogen synthase, a key enzyme in glycogen synthesis, which converts glucose to glycogen in the hepatocytes. In the presence of both frequent hyperglycemia and supraphysiological levels of insulin, glycogen starts accumulating in the hepatocytes (2). When this cycle continues, hepatomegaly, its associated obstructive symptoms, and elevation of liver transaminases start to manifest (2,7). In the current case, the levels of hepatic transaminases increased after intensive insulin therapy was started on day 1, peaking on day 3. When hyperglycemia finally improved on day 4 (average daily blood glucose <200 mg/dL), his transaminases also started to normalize (as shown in Fig. 1). Thus, improving glycemic control is the mainstay of therapy, and complete symptomatic and biochemical resolution have been previously documented. The overall prognosis is good with no progression to liver fibrosis (5,6).

Despite numerous case reports, GH is still widely underrecognized, and diagnosing this condition remains a challenge for both internists and endocrinologists (5,8). GH can be misdiagnosed as nonalcoholic fatty liver disease (NAFLD), the most common cause of hepatitis in the adult diabetic population, since it has indistinguishable ultrasonographic features (9). Despite recent advances in less invasive diagnostic modalities, GH is still largely diagnosed by histopathologic evaluation of liver biopsy samples (9). Pathologic features of NAFLD, such as fibrosis, steatosis, and portal inflammation, are not seen in GH, where hepatocytes are pale, swollen, and have PAS-positive intracytoplasmic inclusions that disappear after digestion with diastase (8,9).

In the appropriate clinical setting, gradient-dual echo liver MRI can help distinguish GH and NAFLD (4). In NAFLD, the presence of hepatic fat content causes a difference in signal intensity from images in the opposed-phase versus images in the in-phase sequence of a T1-weighted liver MRI. This signal intensity difference is not found in conditions where there is no liver fat accumulation, such as GH, supporting the diagnosis of GH instead of NAFLD (4,9).

Although GH and NAFLD should be in the differential diagnosis of patients with hepatomegaly/elevated transaminases and uncontrolled diabetes, other more common and potentially life-threatening conditions should be evaluated first in the appropriate clinical settings. These include ischemic, autoimmune, toxic (acetaminophen, alcohol), infectious (acute viral hepatitis), and genetic (Wilson disease, hemochromatosis) etiologies (7,9). If the above evaluations are unrevealing, other findings that suggest GH include preserved liver synthetic function and elevated lactic acid level (3,5). Unlike other causes of hepatomegaly/elevated transaminases, GH does not usually affect liver synthetic function. In a case series by Chatila et al (2), all GH patients (n = 8) had normal (or mildly elevated) total bilirubin and prothrombin time.

More recently, an elevated lactic acid level has been proposed as an additional feature of GH (3); however, other conditions, such as primary mitochondrial disorder and shock liver, may also cause elevated lactic acid levels and hepatomegaly. Although GH can also cause abnormal, giant mitochondria (8), the absence of stroke-like episodes, epilepsy, deafness, cardiomyopathy, and maternal inheritance of this disorder in our patient suggests that primary mitochondrial disorder is unlikely the cause of out patient's lactic acidosis (3). Furthermore, the fact that improved glycemic control in our patient resulted in improvement of liver transaminases and lactic acid further supports the diagnosis of GH, instead of a primary mitochondrial disorder. Shock liver was ruled out in our case given the fact that our patient never developed circulatory shock during his hospitalization.

In our patient, the initial evaluation was unrevealing, liver synthetic function was preserved, and lactic acid level was elevated, all of which may suggest GH. However, given the rarity of this condition, we pursued an ultrasound-guided liver biopsy to confirm the diagnosis. Based on recent studies (4,7), one can argue that in the case of a negative initial evaluation for common causes of elevated transaminases, along with a preserved liver synthetic function and elevated lactic acid level, a gradient dual-echo MRI followed by a positive response to treatment could be considered as an alternative to liver biopsy (see algorithm in Fig. 3).

CONCLUSION

After excluding common causes of hepatomegaly and elevated liver transaminases, clinicians should consider GH in patients with uncontrolled diabetes treated with insulin therapy. Given the similar ultrasonographic appearance, this condition is commonly misdiagnosed as NAFLD, the most common cause of hepatopathy in patients with diabetes. However, unlike NAFLD, GH does not usually progress to liver cirrhosis, and glycemic control has been shown to improve the hepatomegaly and elevated transaminases in these patients. Recent reports suggest that consistent MRI findings combined with response to

treatment in the appropriate clinic setting may be used as an alternative to liver biopsy in diagnosing GH. Consequently, we propose an algorithm that incorporates less invasive diagnostic methods to guide clinical diagnosis in these cases. However, further studies are needed to validate the accuracy of such an algorithm compared to the standard liver biopsy.

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Abbreviations

DKA	diabetic ketoacidosis
GH	glycogenic hepatopathy
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease

References

1. Mauriac P. Gros ventre, hépatomégalie, troubles de la croissance chez les enfants diabétiques traités depuis plusieurs années par l'insuline. Gaz Hebd Med Bordeaux. 1930; 26:402–410.
2. Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore). 1996; 75:327–333. [PubMed: 8982149]
3. Brouwers MCGJ, Ham JC, Wisse E, et al. Elevated lactate levels in patients with poorly regulated type 1 diabetes and glycogenic hepatopathy: a new feature of Mauriac syndrome. Diabetes Care. 2015; 38:e11–e12. [PubMed: 25614691]
4. Murata F, Horie I, Ando T, et al. 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. Endocr J. 2012; 59:669–676. [PubMed: 22673296]
5. Imtiaz KE, Healy C, Sharif S, et al. Glycogenic hepatopathy in type 1 diabetes: an underrecognized condition. Diabetes Care. 2013; 36:e6–e7. [PubMed: 23264308]
6. van den Brand M, Elving LD, Drenth JPH, van Krieken JHJM. Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus. Neth J Med. 2009; 67:394–396. [PubMed: 20009116]
7. Rogal SS, Ukomadu C, Levy BD, Loscalzo J. A sweet source of abdominal pain. N Engl J Med. 2011; 364:1762–1767. [PubMed: 21542747]
8. Torbenson M, Chen YY, Brunt E, et al. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. Am J Surg Pathol. 2006; 30:508–513. [PubMed: 16625098]
9. Parmar N, Atiq M, Austin L, Miller RA, Smyrk T, Ahmed K. Glycogenic hepatopathy: thinking outside the box. Case Rep Gastroenterol. 2015; 9:221–226. [PubMed: 26269698]

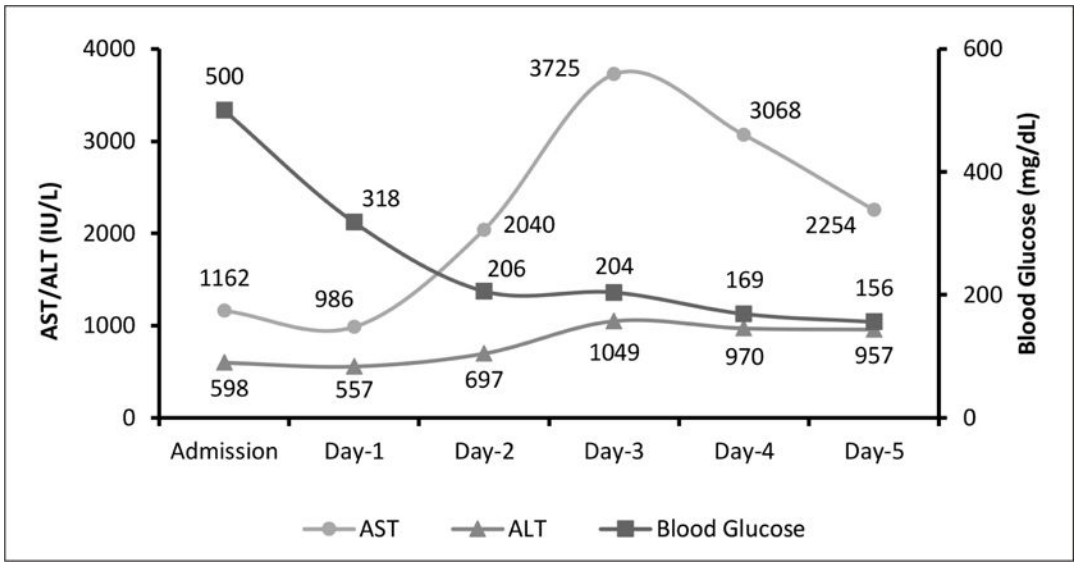

Fig. 1.

Relationship between liver transaminases and mean daily blood glucose (capillary point-of-care blood glucose): *AST* = aspartate aminotransferase (reference range, 10 to 40 IU/L); *ALT* = alanine aminotransferase (reference range, 7 to 56 IU/L).

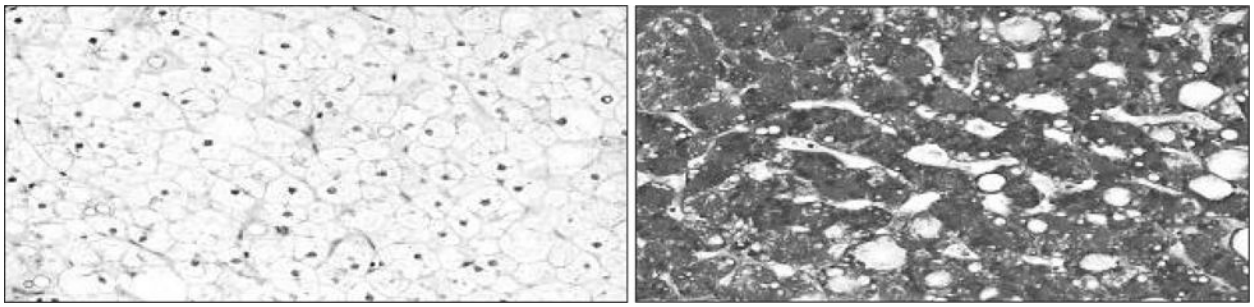

Fig. 2.

Left: liver biopsy showing swollen hepatocytes with cytoplasmic clearing, suggestive of glycogen accumulation (hematoxylin & eosin, × 200). Right: hepatocyte cytoplasm showing accumulation of glycogen, highlighted by periodic acid–Schiff staining (×200).

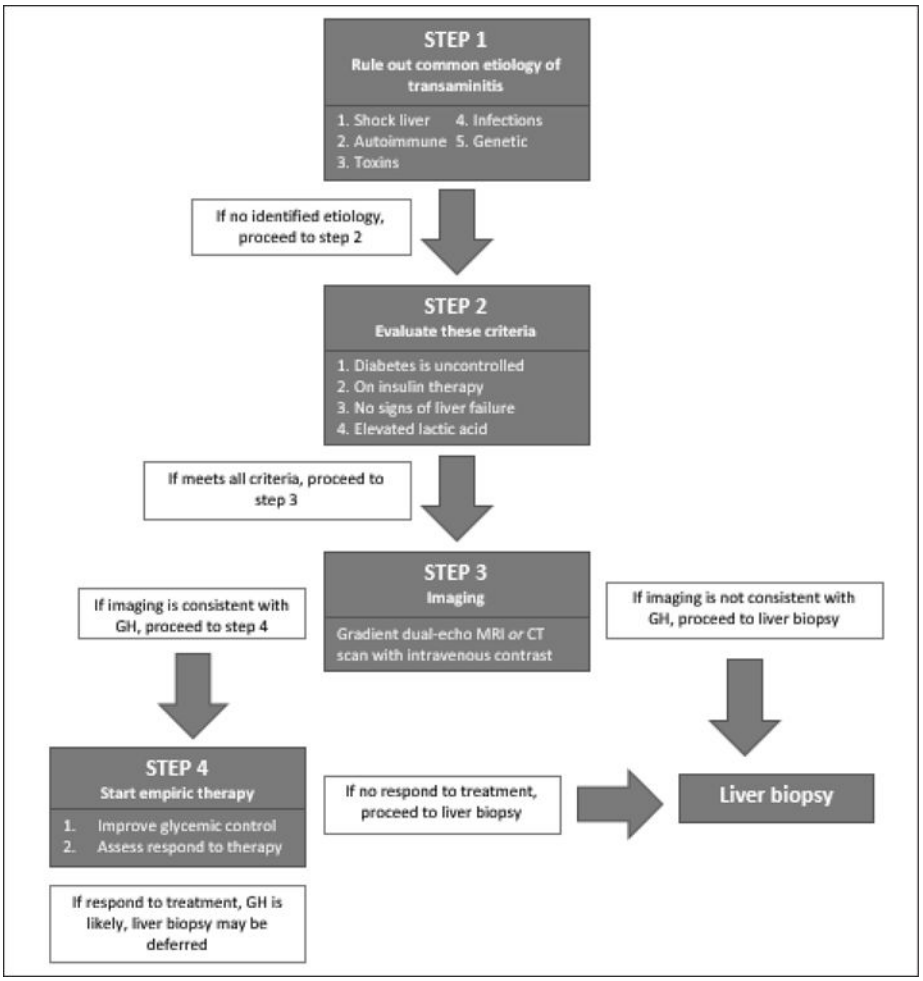

Fig. 3.

Proposed diagnostic algorithm for glycogenic hepatopathy (GH): *CT* = computed tomography; *MRI* = magnetic resonance imaging.