Glycogenic hepatopathy in young adults: a case series

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ABSTRACT

Glycogenic hepatopathy is a rare and underecognized complication in long-standing poorly controlled type 1 diabetes mellitus patients. This is a distinct entity from other causes of hepatomegaly and elevated liver enzymes in diabetics, such as nonalcoholic fatty liver disease. Glycogenic hepatopathy is characterized by the combination of poorly controlled diabetes, acute liver injury with marked elevation in serum aminotransferases, and the characteristic histological features on liver biopsy. It is important to distinguish this entity as it has the potential for resolution following improved glycemic control.

In this report, we describe four cases of adult patients presenting elevated serum transaminases and hepatomegaly with a history of poorly controlled type I diabetes mellitus. One of the patients had also elevated amylase and lipase in the serum, without clinical or imaging evidence of acute pancreatitis. Liver biopsy was performed in all patients and revealed glycogenic hepatopathy. Clinician’s awareness of glycogenic hepatopathy should prevent diagnostic delay or misdiagnosis and will provide better insight and management for this condition.

Key words: Acute hepatitis. Hepatomegaly. Ascitis. Diabetes mellitus. Liver biopsy.

INTRODUCTION

Glycogenic hepatopathy (GH) is a rare and underrecognized condition observed in poorly controlled diabetes (1). It is a diagnosis with unique pathologic features due to hepatocyte glycogen overload that is reversible with good glycemic control (2-4). This is a distinct entity from other causes of hepatomegaly and elevated liver enzymes in diabetics, such as nonalcoholic fatty liver disease. In the differential diagnosis of hepatitis in a young adult with type 1 diabetes mellitus (DM), are considered autoimmune and metabolic liver diseases such as hemochromatosis, Wilson’s disease and nonalcoholic steatohepatitis. Liver biopsy (LB) may play a key role in establishing the correct diagnosis.

The authors propose to describe four cases of GH highlighting the challenges in the differential diagnosis of hepatitis in young adults.

CASE REPORTS

In this report, 4 patients were included, 1 man and 3 women, with a median age of 22 years. All patients had type 1 DM diagnosed in childhood (median duration of 17 years) and a history of poor glycemic control. Patients were admitted for uncontrolled DM (median HbA1c of 10.5%) and for study of hepatomegaly and elevated liver enzymes (median: AST 248 IU/L, ALT 272 IU/L, GGT112 IU/L, ALP 176 IU/L, without elevated bilirubin. The main laboratory features at hospital admission are summarized in table I.

A thorough etiologic study was performed in all cases with negative results, ruling out viral hepatitis, autoimmune, hemochromatosis, alpha 1 antitrypsin deficiency, and Wilson’s disease. Lipid profile was normal as the thyroid and renal function. In order to establish a correct diagnosis, was decided to perform a LB, which confirmed the diagnosis of GH.

During hospitalization, after adequate glycemic control with insulin therapy and adherence to a correct nutritional scheme, there was clinical improvement with progressive normalization of liver biochemical tests.

Following, a report of each case is described.

The first case concerns to a 21-year-old female patient with past medical history of type 1 DM for 10 years, with good metabolic control until a month before admission to the hospital, presenting with abdominal pain and diabetic ketoacidosis (DK) in puerperium. Four weeks earlier, she had an eutocic delivery of a healthy child. During pregnancy she had an excellent metabolic control. After delivery, she stopped medication and insulin therapy for unknown reasons. She had no history of alcohol abuse or smoking. At
admission, the patient had a normal body mass index (BMI) and the single abnormal finding on physical examination was hepatomegaly. At the time of the admission, her AST and ALT were elevated strikingly to 110 IU/L and 120 IU/L, respectively. Abdominal ultrasonography (US) demonstrated an enlarged liver, with uniformly bright echo-texture, suggestive of fatty change. A percutaneous LB was performed showing normal trabecular architecture, without evidence of fibrosis, mild inflammatory infiltrate within portal tracts and absence of steatosis. The hepatocytes were diffusely swollen, with abundant clear cytoplasm, due to accumulation of glycogen (as shown by PAS staining, before and after diastase digestion). Sinusoids were collapsed, both features conferring a "vegetal-like appearance" to liver parenchyma. A diagnosis of hepatic glycogenosis secondary to poorly controlled diabetic disease was suggested.

The patient restarted insulin therapy and her liver function tests returned to normal.

The second case was a 20-year-old female patient with type 1 DM since the age of 2 years, who had longtime poor adherence to therapy, despite of medical efforts. She had a history of multiple admissions for DK due to non-compliance with insulin therapy. She was admitted again with abdominal pain, nausea, vomiting and DK. Her BMI was normal and hepatomegaly was noted in the physical examination. Laboratory tests showed an elevation of the liver enzymes (AST 270 IU/L; ALT 423 IU/L) but also a high amylase and lipase (403 IU/L and 1,358 IU/L, respectively). Abdominal US confirmed hepatomegaly suggestive of fatty change and mild ascites. A CT scan was performed to exclude acute pancreatitis and other causes of abdominal pain, revealing a normal pancreatic parenchyma. A percutaneous LB was performed and showed a normal parenchyma, with no evidence of fibrosis, inflammation or steatosis. The hepatocytes were diffusely swollen with empty-looking cytoplasm and thickened cell membranes, with an overall appearance of plant-like cells. Cytoplasmic deposits of glycogen were shown by PAS staining, followed by digestion by diastase. Altogether, these findings were reported as suggestive of poor metabolic control of diabetic disease.

As soon as metabolic control was achieved, liver and pancreatic enzymes decreased towards normal values. The third case, relates to a 29-year-old female patient hospitalized with a 2 months history of asthenia, anorexia, peripheral edema and epigastric pain, more intense in the last 2 weeks. The patient had poorly controlled type 1 DM diagnosed at the age of 4. She denied the use of drugs, except sporadic alcohol intake and Indian tobacco smoking 6 months before. Her BMI was slightly above normal range. Physical examination revealed hepatomegaly and peripheral edema without jaundice or altered consciousness. Laboratory analysis were compatible with major amino transferase disturbances: AST 910 IU/L and ALT 461 IU/L. Liver synthetic capacity evaluation, revealed low albumin levels (28.8 g/L, normal range 38-51), without coagulopathy. An abdominal US confirmed hepatomegaly without nodules or signs of portal hypertension. An echocardiogram showed a normal heart function and structure. Liver histology (Fig. 1) detected preserved architecture, ballooning and universal clarification of hepatocytes with cell membrane accentuation, giving the hepatocytes a "vegetal-like appearance", with "mosaic" pattern architecture (typically seen in the Mauriac syndrome); also glycogenate nuclei were present.

During hospitalization, there was clinical and analytical improvement, associated with glycemic control after access nutrition and insulin therapy regimen. At a 3 month follow-up visit, all hepatobiliary laboratory abnormalities and hepatomegaly had resolved.

The fourth case concerns to a 22-year-old male patient with type 1 DM, diagnosed at the age of 7. He had a history of previous hospital admissions for DK due to non-compliance with insulin therapy. He was admitted with abdominal pain, nausea, vomiting, diarrhea (without blood, mucus or pus), asthenia and DK. He admitted
that he wasn’t doing insulin therapy in the last 8 months, due to labile working schedule. His BMI was normal and dehydrated mucosa and hepatomegaly were noted in the physical examination. He also had an elevation of the transaminases (AST 226 IU/L; ALT = 109 IU/L). There was no history of taking alcohol or drug except insulin. Abdominal US showed mild hepatomegaly and slightly increased hepatic parenchymal echogenicity. US additionally showed a small nodular lesion in hepatic segment II. An abdominal CT scan was performed and revealed a hypervascular, 22 mm inch, nodular lesion, very suggestive of focal nodular hyperplasia. The patient, did not show any symptom and sign compatible with acute hepatitis. LB in order to elucidate the cause of acute elevation of liver enzyme, was performed and showed normal trabecular architecture, with no evidence of fibrosis, inflammation or steatosis. The hepatocytes had clear cytoplasm and thickened cell membranes, with an overall “mosaic” pattern architecture. Also glycogenated nuclei were diffusely present. These findings were reported as similar to those present in Mauriac syndrome. During hospitalization the patient received extensive diabetes training and his insulin treatment regimen was improved. At a 2 week follow-up visit, hepatobiliary laboratory abnormalities were almost resolved, AST 43 IU/L and ALT 50 IU/L. The patient is currently being followed in outpatient clinic.

DISCUSSION

Type 1 DM is the most common chronic pediatric endocrine metabolic disease with gradually increasing incidence. Some diabetic patients, with poor metabolic control, may develop reversible hepatomegaly and high serum transaminase concentrations, which is rarely reported in the literature (1). Hepatic enlargement in diabetes is usually the result of either glycogenosis or non-alcoholic steatohepatitis (NASH) (3). GH is also defined as the compensation mechanism of the liver that develops in periods of ketosis or poor glycemic control requiring increasing amounts of insulin. It has been reported that GH is the liver response to poor glycemic control in children, adolescents and adults with type 1 DM, while NASH is the most likely diagnosis in adults with obesity and type 2 DM (3). Besides type 1 DM patients, GH may also be present in adults with type 2 DM insulin-dependent and, rarely, after steroid or azathioprine therapy (6).

The influx of glucose into the cell by passive diffusion independent of insulin has been pointed as responsible for GH pathogenesis in diabetic patients with poor metabolic control. In hepatocytes, glucose is converted irreversibly into glucose-6-phosphate (G-6-P) by glucokinase, with the subsequent napping in the hepatocyte. Subsequently, G-6-P is transformed into glycogen by the action of glycogen synthase enzyme. The increase in hepatic glycogen synthesis depends on the presence of a high intracytoplasmic concentration of glucose and the insulin concentration in the environment (3,5).

Although minor abnormalities have been identified in enzymes that control glycogen metabolism (phosphorylase, glucose-6-phosphatase, acid maltase and amylo-1,6-glucosidase), these changes were not considered enough to explain hepatic glycogen storage in GH in the setting of type 1 DM (5).

GH is a hepatopathic state that is more commonly seen during childhood and adolescence than in adulthood and is an underrecognized complication of type 1 DM. It was first described by Mauriac in 1930, in children with brittle diabetes, poor growth, cushing-like features, delayed puberty and hyperlipidemia (7). Later reports described GH without the full spectrum of Mauriac syndrome both in adults and children with brittle diabetes (8,9).

Patients with GH may present with abdominal pain, hepatomegaly or other symptoms like nausea and vomiting. However, the key clinical features are hepatomegaly and a mild to moderate increase in transaminases, although in some cases, the transaminase levels can be dramatically elevated, up to 30 times the upper limit of normal (10). As in case 3, and in to a lesser extends in case 2, very high transaminase levels in the range of acute hepatitis has been reported in patients with GH (4,11). Although the same histological findings have been reported in patients with only mild transaminase elevation, as in case 1 and 4 (2,7,11).

US, usually, demonstrates an enlarged liver, uniformly bright, which does not distinguish glycogen overload from fatty liver (12).

From the available data in the literature, there appears to be an approximately fourfold increase of cirrhosis in patients with diabetes compared to control populations (8). The combination of a history of poorly controlled DM,
acute liver injury indicated sometimes by marked elevation in aminotransferases, and the characteristic GH histological changes on liver biopsy are diagnostic of glycogenic hepatopathy (4,12). Since GH and NASH are hard to differentiate on clinical basis, and have different prognosis, it has been suggested that all patients with diabetes, hepatomegaly and raised liver function tests should undergo a liver biopsy for a definitive diagnosis and evaluation of prognostic factors (3).

The histology of GH demonstrates the following key features: marked glycogen accumulation leading to pale, swollen hepatocytes; no or mild fatty changes; no or minimal inflammation; no or minimal spotty lobular necrosis and intact architecture with no significant fibrosis (12). Endoplasmic reticulum is not prominent. Mitochondria are frequently bizarre and some may contain crystalloids. The histology and ultrastructure of liver biopsies, as reported in the literature, are similar in children and adults (8).

GH is easily treatable in a short time by strict glycemic control (11,13). Overall, it is reported that symptoms can be reversed in 2 to 14 weeks (3). Even in cases with marked transaminase elevations, there is no histologic evidence that the enzyme elevations are due to liver necrosis (11).

Rarely, ascites can also be part of the clinical presentation of GH, as it happened in one of our patients. The underlying pathophysiology is unclear but may involve sinusoidal compression by the glycogen-laden hepatocytes. Ascites also improves with adequate control of blood sugar (12).

Elevation of amylase and lipase ≤ 3 times normal may be non-specific, but elevation of either enzyme to values > 3 times normal is reported to be diagnostic of AP (8). Hyperamylasemia occurs frequently in DK. In contrast, hyperlipasemia is often considered quite specific for the diagnosis of AP. Some reports have identified elevations of lipase in a number of conditions such as acute cholecystitis, intestinal infarction, duodenal ulcer, intestinal obstruction, liver diseases and abdominal traumas (9). A few studies, each based on a small number of cases, have noted hyperlipasemia in DK. Based on the above observations, some authors believe that increased pancreatic enzyme activity (amylase and lipase) in patients with DK, even in the presence of abdominal pain, should not be considered diagnostic of AP since high levels of amylase and/or lipase can be seen in patients with DK without evidence of AP on CT scan. The source of amylase or lipase in DK without AP is not clear. Whether elevation of amylase or lipase or both is extrapancreatic in origin, is speculative and cannot be firmly answered by available evidence. However, several mechanisms have been suggested to account for hyperamylasemia in patients with DK, including salivar amylase, reduced renal clearance of amylase and increased leakage from the acini secondary to neutral and metabolic perturbations (8). Much less is known or postulated about the possible mechanisms of hyperlipasemia in DK, and a few explanations have been offered: as DK causes moderate hypovolemia with elevated BUN and a reduced glomerular filtration rate, this could result in a less efficient handling of lipase; another possibility is the release of nonpancreatic lipolytic enzymes into circulation, the source of which may be the stomach, liver, small bowel, tongue, esophagus or gastroesophageal junction (8). Non-specific elevations of amylase and lipase occur in DK in 16-25% of patients. A diagnosis of AP can only be made by CT scan in patients with DK.

In conclusion, we describe four cases of GH in young adults, with poorly controlled type 1 DM, confirmed by histology, one of which had also significant elevation of amylase and lipase, without AP. It is extremely important to be aware of this pathologic condition because, when suspected and diagnosed, it has a simple and effective treatment, with an impact on the prognosis, as seen in our patients. Clinical awareness of GH should prevent diagnostic delay or misdiagnosis and will provide better insight and management for this condition.

REFERENCES