Glycogenic Hepatopathy: a Rare Disease that can Appear and Resolve Rapidly in Parallel with Glycemic Control

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Glycogenic hepatopathy is an under-recognized disease causing elevations of serum transaminases in patients with diabetes mellitus type 1. It mainly appears in patients with poorly controlled DM. We describe an 18 year old male patient with DM-1 who presented with abdominal pain, hepatomegaly, elevated liver enzymes and lactic acidosis 4 months after changing his insulin treatment regimen. Three months after receiving extensive insulin treatment, the hepatomegaly and all hepatobiliary laboratory abnormalities resolved. To the best of our knowledge, this is the first report showing the rapid appearance and resolution of the disease in parallel with glycemic control.

DM = diabetes mellitus

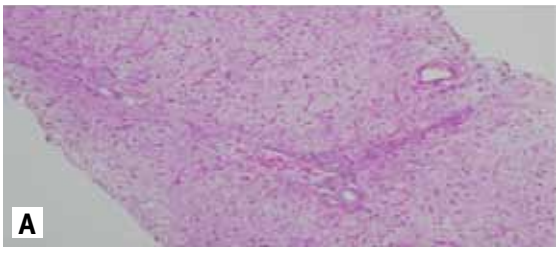
PATIENT DESCRIPTION

A 18 year old Arab male was hospitalized in our hospital with a 3 month history of epigastric and right upper quadrant abdominal pain. He also had DM-1, which was diagnosed at age 10 years. He was treated by means of an insulin pump but the treatment was changed to insulin injections 4 months before his hospitalization. His DM was poorly controlled (HbA1C 11%). He reported no alcohol use, smoking, previous liver disease, family history of liver disease, blood transfusion, exposure to toxins, or cholelithiasis. His other medications included omeprazole (20 mg/day) which he had been taking for one year due to epigastric discomfort.

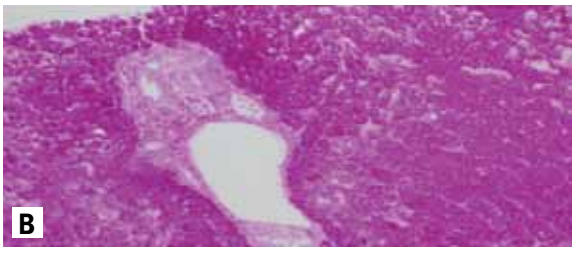
On physical examination the patient was alert without jaundice. He had hepatomegaly without tenderness. No splenomegaly, pedal edema or ascites was noted. Laboratory studies showed a total bilirubin level of 1.4 mg/dl, alanine transaminase 92 U/L, aspartate aminotransferase 144 U/L, alkaline phosphatase 123 U/L, gamma-glutamyl transpeptidase 116 U/L, lactate dehydrogenase 1228 U/L, total protein 6.7 g/dl with albumin 4 g/dl, and normal prothrombin time of 91.9% (international normalized ratio 1.04). The level of lactic acid was elevated (8 mmol/L, normal range 0.5–2.4 mmol/L).

Results of the following serological tests were negative: hepatitis B surface antigen, anti-hepatitis B core immunoglobulin M, anti-hepatitis A virus IgM, anti-hepatitis C virus antibody, anti-cytomagalovirus IgM, anti-Epstein-Barr virus IgM, antinuclear antibodies, anti-smooth muscle antibodies, antimitochondrial antibodies and antineutrophil cytoplasmic antibodies. Serum ferritin level was normal. Ceruloplasmin level was low (15.14 mg/dl, normal range 17–35 mg/dl). C-reactive protein was normal, as was complete blood count. An ultrasound of the abdomen showed "fatty liver, hepatomegaly of 24 cm without splenomegaly."

During hospitalization the patient received extensive diabetes training and his insulin treatment regimen was changed. After 7 days of hospitalization the liver enzymes were still elevated. The patient was discharged for follow-up in our unit. One month later a liver biopsy [Figure] showed preserved architecture with no evi-



[A] The histology demonstrates normal architecture with diffuse hepatocellular change characterized by pale hepatocytes with cytoplasmic rarefaction and accentuation of the cell membranes. Few glycogenated nuclei are noted. There is no inflammation.



[B] Abundant cytoplasmic glycogen deposits can be demonstrated by PAS stains, which disappear after digestion with diastase

dence of inflammation, fibrosis or steatosis. Staining for copper was negative. The hepatocytes were pale and distended with vacuolization of their cytoplasm. Staining with periodic-acid Schiff showed diffuse cytoplasmic positivity that was eliminated following diastase digestion [Figure]. This pattern denotes glycogen storage.

At a 3 month follow-up visit all hepatobiliary laboratory abnormalities had resolved and a physical examination confirmed the disappearance of hepatomegaly.

COMMENT

The clinical manifestations of glycogenic hepatopathy include hepatomegaly, abdominal pain, and other symptoms such as nausea and vomiting [1]. Elevated serum transaminases are frequent in diabetes mellitus type 1 as well as type 2, and are mostly caused by non-alcoholic fatty liver disease. An important and underdiagnosed condition is GH. The differentiation between the two conditions is critical since the treatment and the prognosis are very different. Glycogenic hepatopathy appears to be under-recognized by clinicians, radiologists and pathologists, even though this entity has been described several times over the years in the medical literature [1]. The combination of a history of poorly controlled diabetes mellitus, acute liver injury indicated sometimes by marked elevation in aminotransferases, and the characteristic histological changes on liver biopsy are diagnostic of glycogenic hepatopathy [2].

The key finding in GH is glycogen accumulation in the liver, causing hepatomegaly and elevated liver enzymes, especially transaminases. Hepatomegaly and elevated transaminases are frequent findings [2,3]. All patients with GH are on insulin therapy and virtually all patients have type 1 DM, although GH has been reported in type 2 [3].

NAFLD can progress to cirrhosis, whereas GH has a much better prognosis since liver fibrosis does not develop. Liver biopsy should be considered, especially when transaminase flares occur in non-obese patients with type 1 DM [3]. Unlike most cases of NAFLD, glycogenic hepatopathy can be reversed by improving glycemic control or by pancreas transplantation [4].

Additionally, on computed tomography scan the liver is hypodense in NAFLD while in GH it is hyperdense. Also, the bright liver on CT scan without the administration of contrast can be a clue to the diagnosis of GH [5].

Interestingly, the patient's symptoms appeared only 4 months after he changed his insulin treatment regimen, and resolved rapidly after extensive insulin therapy. This case suggests that GH can appear even after a short time of uncontrolled DM-1, but fortunately can also resolve a short time after improving glycemic control. According to our knowledge, this case is the first report in the literature of GH that developed within 4 months of uncontrolled DM-1.

In summary, GH is an underdiagnosed disease that appears primarily in patients with uncontrolled DM-1. It can be confused with NAFLD. The condition can develop rapidly and is rapidly reversible after improving glycemic control.

GH = glycogenic hepatopathy

NALFD = non-alcoholic fatty liver disease

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Erratum

In the February issue, the authors of the article "The Games Go On: British Medical Journals Play Politics, Again" were Yehuda Shoenfeld, Joshua Shemer, Gad Keren, Yoram Blachar, Leonid Eidelman and Malke Borow, and not The Editorial Office, *IMAJ*, as written (2012; 14: 82-3).