Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus

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ABSTRACT

Glycogenic hepatopathy (GH) is a rare cause of serum transaminase elevations in type 1 diabetes mellitus (DM). We describe a 29-year-old woman with a history of poorly controlled type 1 DM who presented with hepatomegaly and severe transaminase flares. Liver histology confirmed GH, with glycogen accumulation due to severe fluctuations in both glucose and insulin. GH can be regarded as an adult variant of Mauriac’s syndrome. Despite severe laboratory abnormalities, it does not cause liver cirrhosis. Treatment consists of improving glycaemic control.

KEYWORDS

Glycogenic hepatopathy, liver glycogenosis, Mauriac syndrome, type 1 diabetes mellitus

INTRODUCTION

Elevated serum transaminases in type 1 as well as type 2 diabetes mellitus (DM) are most frequently caused by non-alcoholic fatty liver disease (NAFLD), with possible progression to liver cirrhosis.1 Glycogenic hepatopathy (GH) is a rare cause of elevated serum transaminases, mostly confined to type 1 diabetics. We present a case of GH in a patient with poorly controlled type 1 DM. The recovery of severe transaminase elevations in this patient illustrates the more benign course of GH as compared with NAFLD.

CASE REPORT

A 29-year-old female with a 14-year history of poorly controlled type 1 DM (HbA1c between 7.2 and 15.3%), complicated by recurrent ketoacidotic dysregulations, developed severe increases in transaminase levels that were followed by recovery to near normal levels (figure 1) during periods of better metabolic control. Physical examination revealed hepatomegaly, which was confirmed by abdominal tomography. Laboratory analysis was compatible with major aminotransferase disturbances (figure 1), with concurrent increases in gamma-glutamyl transferase (1467 U/l, normal <35) and alkaline phosphatase (316 U/l, normal <120). Liver synthetic capacity as measured by serum albumin (35 g/l, normal 35 to 35) and coagulation tests (activated partial thrombin time 23 sec, normal <35) remained normal. Her medical history included an eating disorder (anorexia nervosa) and repeated bouts of pancreatitis and abscess formation in liver, m. psoas and the peritoneal cavity caused by Staphylococcus aureus and Candida albicans. Despite extensive investigation no immune deficiency was found. When she was 29 years old she had a flare with grossly elevated liver enzymes and a liver biopsy was performed. Pathological examination of the liver biopsy specimen showed extensive glycogen accumulation suggesting an inherited glycogen storage disorder (GSD). However, GSD type Ia, lc, lc and III were excluded by mutational analysis and enzyme studies.

What was known on this topic?
Glycogenic hepatopathy (GH) has been described in literature, but reports remain scattered. Only recently, we are beginning to acknowledge and understand this entity.

What does this add?
Intermittent elevated liver transaminases in diabetes mellitus are not necessarily caused by non-alcoholic fatty liver disease, but can be due to GH, a condition with a far better prognosis. Clinicians’ awareness of GH should prevent diagnostic delay, as was the case in our patient, and will provide better insight into the prevalence of GH.

The flares with gross elevations of the serum transaminases persisted, but liver ultrasound consistently showed normal liver parenchyma hepatopetal flow in the portal and hepatic veins. Remarkably, transaminase flares followed glucose dysregulations, with recovery several days after glucose normalisation.

At the age of 30 years liver biopsy was repeated. In line with the previous biopsy there was glycogen accumulation, characterised by hepatocyte swelling, accentuation of cell membranes due to cytoplasmic rarefaction and strongly positive periodic acid Schiff (PAS, stains polysaccharides) staining (figure 2). After diastase digestion, which selectively degrades glycogen, PAS staining was no longer positive, confirming that glycogen accumulation was responsible for the findings.

From the results above we can conclude that this patient is most likely suffering from an acquired GSD. In this patient, it is most probably related to the poorly controlled type 1 DM in a condition called glycogenic hepatopathy (GH). In retrospection, this diagnosis could have been established from the first liver biopsy.

**DISCUSSION**

GH was first described by Mauriac in diabetic children as part of a syndrome including growth retardation, cushingoid habitus and delayed puberty. It is now becoming clear that the liver defects observed in Mauriac’s syndrome can occur without the syndromal features in adults with type 1 DM. GH is most probably a rare condition and many clinicians are unaware of this differential diagnosis. As a result, incidence and prevalence are unknown and it most likely goes unrecognised, as illustrated by our patient.

The key finding in GH is glycogen accumulation in the liver causing hepatomegaly and elevated liver enzymes, especially transaminases. A literature survey on reports of GH shows that especially hepatomegaly and elevated transaminases are very frequent findings. All patients with GH are on insulin therapy and virtually all patients have type 1 DM, although GH has been reported in type 2 DM. Liver biopsy shows ballooning of hepatocytes and glycogen deposition causing cytoplasmic rarefaction and cell membrane accentuation. PAS staining is strongly positive.

An essential element in the pathophysiology of GH is wide fluctuations in both glucose and insulin levels. High serum glucose levels cause an insulin independent inflow of glucose in hepatocytes where it is rapidly phosphorylated, trapping it in the cell. Subsequent treatment of high glucose levels with insulin causes the trapped glucose to polymerise to glycogen. Glycogen production persists for some time after insulin levels have declined. The alternation of high glucose and insulin levels in poorly controlled DM causes glycogen accumulation. Therefore, it comes as no surprise that this syndrome was first described in 1930, only shortly after insulin treatment had become available.
It is unclear why only a small subset of patients develop GH. It could be speculated that defects exist in genes that encode regulatory proteins, such as laforin, causing mild or no abnormalities in normal individuals, but marked glycogen storage under certain conditions such as glucose and insulin fluctuations. These proteins could regulate the activity of glycogen synthase and/or glucose-6-phosphatase. Treatment of GH consists of improving glycemic control. Adequate management of glucose and insulin levels can result in complete remission of clinical, laboratory and histological abnormalities. Unfortunately, in our patient, despite treatment with continuous subcutaneous insulin infusion, poor glycemic control and elevated liver enzymes persisted due to her eating disorder. An important differential diagnosis to consider in diabetics with liver disturbances is NAFLD. NAFLD can develop in both type 1 and type 2 DM, regardless of insulin treatment. Persistent and relatively mild disturbances in liver enzymes favor NAFLD, whereas transaminase flares are more compatible with GH. Because liver ultrasound is similar in NAFLD and GH, a final distinction between GH and NAFLD can only be made with a liver biopsy. It is important to distinguish both conditions as NAFLD can progress to cirrhosis whereas GH has a much better prognosis. Especially in patients with transaminase flares, liver biopsy should be considered. Clinicians’ awareness of GH will cause less diagnostic delay and more insight into the prevalence of this presumably rare but completely reversible disorder. To further enhance our knowledge on this syndrome we wish to establish a registry for such patients and we welcome information on additional patients.

CONCLUSION

GH can cause severe, but reversible elevations of serum transaminase levels in patients with poorly controlled type 1 diabetes due to liver glycogen accumulation. It is important to distinguish it from NAFLD because the prognosis differs. Especially in patients with transaminase flares, liver biopsy should be considered. Clinicians’ awareness of GH will cause less diagnostic delay and more insight into the prevalence of this presumably rare but completely reversible disorder. To further enhance our knowledge on this syndrome we wish to establish a registry for such patients and we welcome information on additional patients.

REFERENCES
