Review Article

The Bright Liver of Glycogenic Hepatopathy

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Abstract

Background : Glycogenic Hepatopathy (GH) is an underdiagnosed complication of poorly controlled diabetes. It is reversible and has a better prognosis in comparison to Non-alcoholic Fatty Liver Disease. Through this review, the authors wish to discuss the various salient features of this condition.

Key words : Glycogenic Hepatopathy, Diabetes Mellitus, Non-alcoholic Fatty Liver Disease

Glycogenic Hepatopathy (GH) is an under-diagnosed complication seen in children and young adults with poorly controlled T1DM and a few patients with T2DM[1,2]. It causes hepatomegaly and a transient rise of liver enzymes due to reversible accumulation of glycogen in hepatocytes. It is confirmed with the help of Liver Biopsy and staining of glycogen using Hematoxylin & Eosin (H&E) stain.

Etiology :

Glycogenic Hepatopathy was first explained by Pierre Mauriac in 1930 in a child with brittle T1DM who presented with cushingoid features, hepatomegaly and poor growth, as part of the Mauriac Syndrome[3,4]. Other terminologies which were used before 'glycogenic hepatopathy' are 'hepatic glycogenosis', 'hepatic glycogen storage disease' and 'glycogen storage hepatomegaly'[5-10]. Torbenson and colleagues formulated the term 'Glycogenic Hepatopathy' in 2006, which has now been adopted worldwide[10].

Glycogenic Hepatopathy has also been noticed in patients with dumping syndrome after gastrectomy, anorexia nervosa, azathioprine use, high dose corticosteroids and insulin usage[9,11-13].

Epidemiology :

Exact statistical data of incidence and prevalence of Glycogenic Hepatopathy (GH) are not known; much of the information is through reported case studies, case series, retrospective cohort study, and more recently case-control studies[4,15]. The prevalence of liver disease among diabetics is approximated to be between 17% to 100%, with NAFLD and GH being the most common[16]. Around 98% of GH cases have been reported in T1DM while the rest 2% in T2DM. Out of the reported cases 62% were females, while 38% were males, indicating a slight female predominance, adolescence being the most common age group[17].

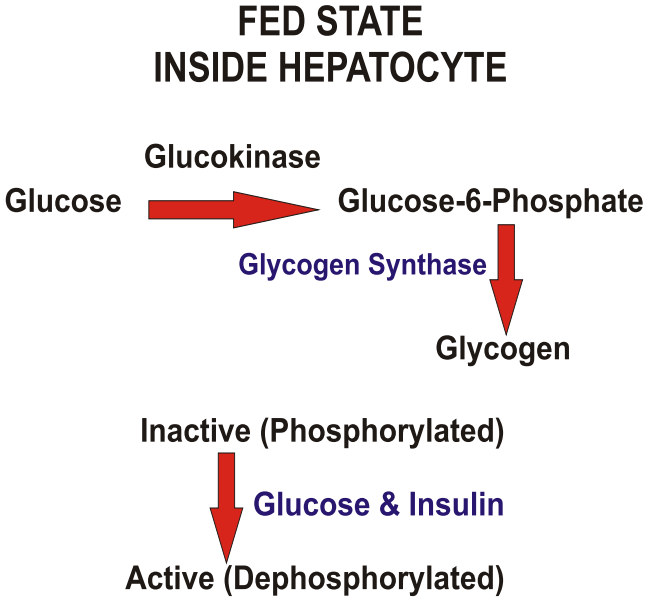
Editor's Comment :

- Glycogen Hepatopathy (GH) is an underdiagnosed complication of poorly controlled Diabetes Mellitus.
- It occurs due to accumulation of glycogen in hepatocytes.
- GH leads to hepatomegaly and derangement of Liver Function Tests.
- GH is reversible with adequate glycemic control.

Pathophysiology :

The pathophysiology of GH is unclear. It is probably due to the glycemic variation with hyperglycemia, hypoglycemia and hyper-insulinization. The disease occurs when long standing hyperglycemia is treated with supra-physiological amounts of insulin[10].

After meal, the liver takes up glucose via GLUT 2 and uses it for fuel and the excess to be converted into glycogen, the reservoir form of glucose. The balance of glycogen levels in the liver is maintained by glycogenosis and glycogenolysis[19].



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With continuous glycogen storage, hepatomegaly may develop within a few days to week and can reverse rapidly once the hyperglycemia is controlled[21].

Clinical Presentation[17,26] :

- Asymptomatic elevated liver enzymes associated with symptoms of hyperglycemia.
- Symptoms of diabetic ketoacidosis like nausea, vomiting or abdominal pain.
- Children can present with delayed puberty, growth failure and hepatomegaly.
- Abdominal pain
- Hepatomegaly, which can be tender.
- Ascites is uncommon; may be due to sinusoidal compression by the enlarged glycogen-laden hepatocytes.

Biochemical Features :

The liver synthetic functions are preserved. However, in more than 90% of patients with hepatomegaly, there has been transaminitis without an increase in Alkaline Phosphatase. This is due to the cell membrane injury rather than necrosis.

Histopathology :

Liver Biopsy is considered to be the gold standard for the diagnosis of Glycogenic Hepatopathy. Typical feature is swollen hepatocytes. The H&E stain shows enlarged and pale hepatocytes with multiple glycogenated nuclei. Empty hepatocytes ("Ghost Cells") are seen when Diastase enzyme is added to the Periodic Acid-Schiff (PAS) stained specimen due to enzymatic degradation of glycogen[22].

Imaging :

Ultrasound Imaging :

It cannot differentiate GH from NAFLD and shows hepatomegaly with uniform echogenicity.

Computed Tomography Scan :

It can help in differentiating GH from fatty liver. The glycogen loading of the liver in GH appears hyperdense on the CT scan whereas, fatty liver appears hypodense (Fig 1). The "Shining Liver" on CT scan is the important clue that points to a diagnosis of Glycogenic Hepatopathy. The other cause of increased hepatic attenuation is hemochromatosis[23].

Magnetic Resonance Imaging (MRI) :

Dual-Echo MRI detects deposition of glycogen by identifying low intensities on T2 weighted images and differentiates GH from Inflammatory Fatty Liver Disease and NAFLD[23,27]. A new modality, 13C Magnetic Resonance Spectroscopy (MRS), can provide quantitative information of hepatic glycogen deposits[28].

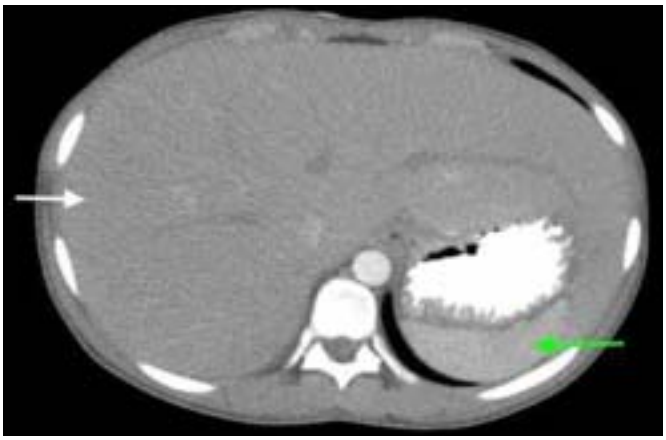

Fig 1 — Transverse view of Abdominal CT scan showing massive hepatomegaly (white arrow) with mild diffuse nonspecific hepatic steatosis as indicated with the difference in intensity between liver (white arrow) and spleen (green arrow) (Source: Yousaf 2020)

Differential Diagnosis :

Other diseases that can cause hepatomegaly with transaminitis in patients with Diabetes Mellitus include:

- Non-alcoholic Fatty Liver Disease (NAFLD)
- Viral hepatitis
- Autoimmune hepatitis
- Celiac disease
- Wilson disease
- Hemochromatosis

Management :

Glycogenic Hepatopathy is benign and reversible. Improved glycemic control is the most important part of effective management; with which both clinical and biochemical features of GH can reverse within days to weeks[24]. The exact glycemic control is not yet established but aggressive insulin treatment is not warranted. In a case report published by Parmar, *et al* only 0.6% improvement in HbA1c led to the relief of abdominal pain and fall in liver enzymes[25].

Prognosis :

With good glycemic control, GH is completely reversible. Being a benign condition, it has a very good prognosis, and must be differentiated from NAFLD because the latter can progress to fibrosis while GH does not.

Discussion

Glycogenic Hepatopathy remains an under-recognized complication of T1DM characterized by severe transaminitis and hepatomegaly, which is reversible with

adequate glycemic control. Glycogenic Hepatopathy must be differentiated from NAFLD as prognosis differs. Early diagnosis and appropriate treatment by achieving good glycemic control will lead to a very favourable prognosis.

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