中文題目：糖尿病合并肝指數異常之困難診斷：糖原性肝病

英文題目：Glycogenic hepatopathy: a concealed diagnosis

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Introduction

Glycogenic hepatopathy (GH) is a rare yet reversible complication of poor glycemic control in patients with diabetes mellitus, characterized by conspicuous rise in serum transaminases and hepatomegaly due to intrahepatic glycogen deposition. [1] Herein, we report a challenging case of a 12-year-old girl with poorly controlled type 1 diabetes mellitus presenting with recurrent diabetic ketoacidosis and transaminitis.

Case report

A 12-year-old girl with a 5-year history of type 1 diabetes mellitus with poor glycemic control, complicated with recurrent diabetic ketoacidosis, presented with a 5-months history of elevated liver transaminases. Her glycemic control was suboptimal due to drug non-adherence, unwillingness of carbohydrate counting and inadequate delivery of insulin doses. Her HbA1c was 11.3% in Feb 2021. Continuous glucose monitoring (CGM) demonstrated severe glucose surges along with prominent hypoglycemic variations. (Figure 1)

She was not on any medications other than insulin. There was no fever, rash, history of jaundice, animal contacts, blood transfusion, alcohol, or herbal ingestions. There was no family history of liver disease or autoimmune disorder.

Her body mass index was 18.269 kg/m^2. Her weight was 33.1 kg, which was within normal growth parameter (10th percentile), but a height of 134.6cm that was below average (< 5th percentile). No stigmata of chronic liver disease were identified. The remainder physical findings were unremarkable. No signs of pubertal changes were observed.

Laboratory analyses (Table 1) revealed elevated serum transaminase, compatible with acute hepatitis. Her hepatic synthetic function, including prothrombin time, total bilirubin and albumin were within normal limits. The serology profiles for viral hepatitis A, B, C, Epstein-Barr virus, herpes simplex virus and cytomegalovirus were negative. Thyroid function tests and screening of metabolic liver disease, including serum ceruloplasmin, copper, iron profile and alpha-1-antitrypsin were all

unremarkable. Ultrasound of the abdomen revealed enlarged liver with bright echogenicity and smooth surface. No splenomegaly or ascites was detected.

She had seropositivity for anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA), where prednisolone 2.5mg daily was introduced under the impression of autoimmune hepatitis. It was followed by a transient reduction in serum transaminase. However, she had another sharp incline in serum transaminases during the follow-up.

She ultimately underwent liver biopsy, which demonstrated steatosis with mild portal fibrosis and lobular peri-cellular fibrosis, consistent with non-alcoholic fatty liver disease (NAFLD). The NAFLD activity score is 4 points (steatosis grade: 1+, lobular inflammation: 1+, prominent ballooning: 2 = 4 points), indicating moderate activity.

Additionally, glycogenated nuclei were found in the hepatocytes. Periodic acid-Schiff (PAS) staining was positive for intracytoplasmic glycogen deposits (Figure 2), which vanished after diastase digestion, confirming glycogenic hepatopathy (GH). There was no evidence of autoimmune hepatitis. The patient was finally diagnosed with concomitant NAFLD and GH. Corticosteroid was discontinued and glycemic control with multidisciplinary team approach were reinforced.

Laboratory studies	Results	Reference range
Liver function tests		
AST	631	
ALT	927	
TBI	0.8	
DBI	0.25	
ALP	192	
GGT	212	
Alb	3.9	
PT/INR	9.4/0.89	
Lipid profile		
TG	219	
HDL	93	
LDL	112	
Viral serologies		
HBsAg	Negative	
HBc-IgM	Negative	

Anti-HCV	Negative	
Hepatitis A, IgM	Negative	
Epstein-Barr virus IgM	Negative	
HSV IgM	Negative	
CMV IgM	Negative	
Autoimmune hepatitis		
Antinuclear antibody (ANA)	Diffuse 1:320 Speckle 1:80	
Anti-smooth muscle antibody (ASMA)	Positive (20x)	
Antimitochondrial antibody (AMA)	Negative	
IgG	598	
IgA	169	
IgM	97	
Copper	845 µg/L	700-150
Ceruloplasmin	22.8 mg/dl	
Alpha-1-antitrypsin (AAT)	105 mg/dl	
Iron level (Fe)	96 µg/dL	
Total iron binding capacity	229 µg/dL	
Ferritin	91.96	
Thyroid function tests		
TSH	1.96 uIU/ml	
Free T4	1.13 ng/dl	

Table 1: Laboratory results

Discussion

Glycogenic hepatopathy (GH) is characterized by the constellation of poor glycemic control, marked liver enzymes derangement and typical histological findings on liver biopsy. Date back to the early 1930's, GH was first described as a component of Mauriac syndrome, which encompass of brittle diabetes, growth retardation, delayed puberty, and cushingoid features. These features were discovered after the introduction of insulin. Though rare, the incidence of GH is believed to be underrecognized.

In hyperglycemic status, glucose passively enters the hepatocyte via insulin-independent process and is subsequently converted by glucokinase into glucose-6-phosphate (G-6-P). G-6-P is transformed into glycogen by activation of glycogen synthase. In the presence of frequent hyperglycemia and supraphysiologic doses of insulin administration, the dephosphorylation of both glycogen synthase

and glycogen phosphatase were enhanced. These imbalance in glycogen production and degradation leads to abnormal glycogen deposition inside the hepatocytes. This results in hepatocytes swelling and hence, hepatomegaly and leakage of transaminases.

Clinical manifestation of GH ranged from asymptomatic elevation of liver enzymes to assorted signs and symptoms of hyperglycemia and hepatitis. Drastic elevation of liver enzymes up to 30 times the upper normal limit has been reported. The most common finding is tender hepatomegaly, which results from the distension of Glisson's capsule. Excessive glycogen accumulation inside the hepatocytes eventually leads to sinusoidal compression and hence the development of ascites.

Ultrasound usually showed liver enlargement and mild hyperechoic liver parenchyma, however, it does not distinguish GH from NAFLD. Sweetser and Kraichely described that non-contrast computed tomography could be useful in detection of GH, with GH demonstrating a hyperdense liver, as compared with a hypodense liver in NAFLD. [2] Gradient dual-echo magnetic resonance imaging could provide additional quantitative information.

There are many potential diagnoses of elevated serum transaminases in patients with diabetes mellitus. The lists of differential diagnosis include NAFLD, viral hepatitis and autoimmune hepatitis should all be considered. (Table 2) The distinction between GH and other causes of liver disease is difficult to made on clinical basis. Therefore, liver biopsy served as the gold standard for the diagnosis of GH.

The hallmark of GH is its potential reversibility with intensive glycemic control. Several studies have confirmed that patients with GH showed clinical and biochemical resolution in 2 to 14 weeks with improved glycemic control. Successful reversal of GH has also been reported in post-pancreatic transplantation. [3] Palmar et al. described a case of GH that demonstrated symptomatic relief and normalization of liver enzymes with just a subtle 0.6% reduction of HbA1c. [4]

The prognosis of GH is excellent, as it was not known to progress to fibrosis. However, recurrence of GH has been documented in cases with poor glycemic control and repeated episodes of DKA. Therefore, follow-up of GH patients is warranted in addition to the maintenance of strict glycemic control.

	Glycogenic hepatopathy (GH)	**Nonalcoholic fatty liver disease (NAFLD)**	**Autoimmune hepatitis (AIH)**
Clinical presentation	• Asymptomatic • Elevated liver enzymes up to 30 times ULN • Hepatomegaly • Symptoms of hyperglycemia or hepatitis	• Asymptomatic • Liver enzymes elevation (<5 times ULN)	• Asymptomatic • Elevated liver enzymes up to 10 times ULN • Extrahepatic syndromes: thyroiditis, Sjogren's
Imaging	• US: increased echogenicity • Non-contrast CT: hypodense liver • Dual-echo MRI: isointense on in-phase and out-phase; low intensity on subtraction	• US: increased echogenicity • Non-contrast CT: hyperdense liver • Dual-echo MRI: low intensity on in-phase, high intensity on out-phase and subtraction	No characteristic imaging features
Histology	• Intracytoplasmic glycogen deposition • Diastase digestion of glycogen	• Steatosis • Lobular inflammation (NASH) • Varying degree of fibrosis	• Interface hepatitis, portal lymphoplasmacytic infiltrates • Varying degree of fibrosis
Prognosis	Reversible with glycemic control	May progress to fibrosis and cirrhosis	May progress to fibrosis and cirrhosis

Table 2: Comparison of GH, NAFLD and AIH. ULN: upper limit of normal, US: ultrasound, CT: computed tomography.

Conclusion

GH should be considered in the broad differential diagnosis of transaminitis in patients with diabetes mellitus. Nevertheless, GH cannot be elucidated based on clinical basis or ultrasound alone. Liver biopsy plays a pivotal role in diagnosing GH. Clinician awareness of this entity is crucial to facilitate timely diagnosis and subsequent therapeutic implementations, given its potential reversibility with

improvement in glycemic control.

References:

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