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CASE REPORT

Toxicology

Glycogenic hepatopathy following attempted suicide by long-acting insulin overdose in patient with type 1 diabetes

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Abstract

Patients with poorly controlled insulin-dependent type 1 or type 2 diabetes rarely present with glycogenic hepatopathy, which is characterized by hepatomegaly and liver enzyme abnormalities. Glycogenic hepatopathy occurs as a consequence of excessive accumulation of glycogen in hepatocytes caused by insulin. We report a young male patient with type 1 diabetes mellitus who developed glycogenic hepatopathy following a suicide attempt by insulin overdose via subcutaneous injection. The patient's medication/nutrition compliance and adherence to insulin were poorly controlled due to comorbid schizophrenia. Our patient required a large amount of continuous glucose to maintain euglycemia for persistent intractable hypoglycemia induced by overdose of long-acting insulin. On admission day 4, the patient presented elevated transaminases, hepatomegaly, and lactic acidosis. Computed tomography revealed swollen liver parenchyma with a diffusely high absorption. The patient gradually recovered without any medical intervention except for adequate control of blood sugar and was moved to a psychiatric ward on day 8 for schizophrenia management. This report may help emergency physicians be aware of the common symptoms, clinical course, and pathophysiology of glycogenic hepatopathy. Doctors should include glycogenic hepatopathy in the differential diagnosis of abnormal liver enzymes and hepatomegaly for those with poorly controlled insulin-dependent diabetes mellitus or unstable blood sugar levels due to insulin overdose like our patient.

KEYWORDS

diabetes mellitus, drug overdose, glycogen, hypoglycemia, insulin, liver disorder, schizophrenia

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1 | INTRODUCTION

Glycogenic hepatopathy is an uncommon complication in patients with poorly controlled insulin-dependent type 1 or type 2 diabetes. The pathophysiology of glycogenic hepatopathy is glycogen accumulation within hepatocytes, leading to hepatic dysfunction with elevated liver enzymes along with hepatomegaly.[1,2] During hyperglycemic periods, glucose freely infiltrates hepatocytes, activating synthesis of glycogen, which is further amplified by dosing with insulin to supraphysiologic levels. Because emergency physicians still under recognize glycogenic hepatopathy in the clinical setting, differentiating glycogenic hepatopathy from non-alcoholic fatty liver disease is important. Here, we report an uncommon case of glycogenic hepatopathy that occurred in a patient with poorly controlled type 1 diabetes mellitus who attempted suicide by injecting himself with long-acting insulin. Due to the sustained release of long-acting insulin in the subcutaneously injected overdose, prolonged continuous infusion of concentrated glucose was required, which might have triggered the development of glycogenic hepatopathy in this patient. Although glycogenic hepatopathy is a rare condition, emergency physicians should be aware of the condition as a differential diagnosis for hepatic dysfunction during the follow-up period of patients with unstable glucose levels treated with insulin.

2 | CASE REPORT

A 25-year-old man was brought to our hospital by his family after he attempted suicide by injecting himself subcutaneously with a massive insulin dose, estimated quantities of 3600 units of insulin glargine and 2100 units of insulin lispro. The patient was experiencing a cold sweat and was feeling groggy. Past medical history of the patient included type 1 diabetes mellitus diagnosed at 11 months old and treated with insulin for 24 years. He was also diagnosed with comorbid schizophrenia at age 23 and had been treated with brexpiprazole for 2 years. Four months prior to admission, the patient fell from an 8-meter height, self-injected an insulin overdose in a suicide attempt, and was hospitalized for 3 months. After discharge, the patient discontinued his antipsychotic treatment and continued to suffer from suicidal urges.

The vital signs and physical examination results at his initial visit were as follows: blood pressure was 136/83 mmHg, pulse was 110 beat/min, respirations were 23/min, temperature was 36.1°C, and a blood sugar level of 50 mg/dL. His consciousness level was alert without neurological defects. Cardiovascular and respiratory examinations were unremarkable. An injection scar was found on his right abdomen. Psychiatric examination revealed that the patient had auditory hallucination.

Laboratory data were as follows: white blood cells, 15,400/μL; hemoglobin, 16.1 g/dL; platelet, 270,000/μL; serum albumin, 4.3 g/dL; aspartate transaminase, 22 IU/L; alanine aminotransferase, 16 IU/L; total-bilirubin, 0.77 mg/dL; creatinine, 0.59 mg/dL; urea nitrogen, 16.7 mg/dL; sodium, 144 mmol/L; potassium, 2.6 mmol/L; and chlorine, 106 mmol/L. Arterial blood gas analysis on ambient air showed a pH of 7.4, PaO_2, 118.3 mmHg, $PaCO_2$ 33.9 mmHg, HCO_3^- 22.0 mmol/L, base excess −3.5 mmol/L, and lactate 3.2 mmol/L. The patient was admitted to the emergency intensive care unit for careful monitoring and maintenance of blood sugar and electrolytes. The patient complained of occasional sweating, palpitation due to tachycardia around 120–140 bpm, and right rib pain. Because the blood sugar levels were sustained low, the patient required an additional dose of glucose to maintain euglycemia despite initiation of oral intake and continuous intravenous injection of a 17.5% solution of glucose infusion via central venous catheter (Figure 1). The first immunoreactive insulin measurement was 58,525 μU/mL, which gradually decreased and improved to within a normal range on day 7. The patient was given about 900 g of glucose/day for the first 4 days. On the day 4 of admission, the patient complained of general fatigue, persistent right hypochondralgia, abdominal discomfort, and appetite loss. Follow-up blood chemistry confirmed elevated transaminases. Aspartate aminotransferase, alanine transaminase, and lactate were 1441 IU/L, 799 IU/L, and 4.9 mmol/L, respectively. Abdominal ultrasound demonstrated homogenous enlargement of the liver. A sectional computed tomography (CT) scan revealed that the liver parenchyma was swollen

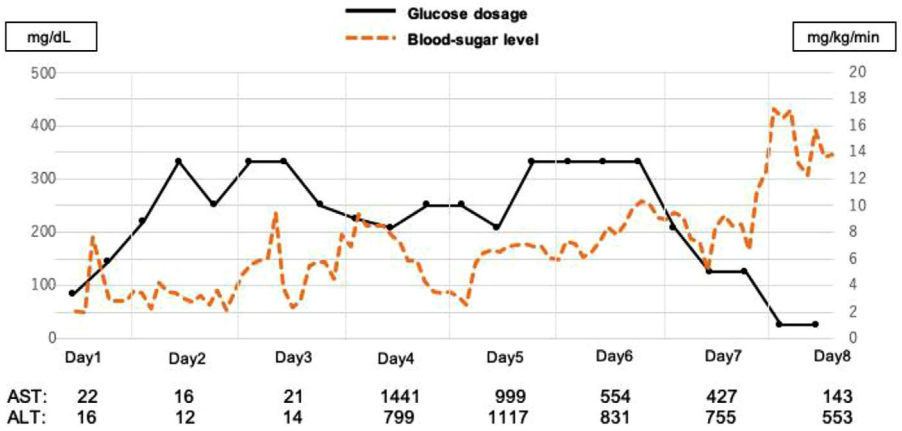

FIGURE 1 The sequential record shows the blood sugar concentration and the average of the 8-hour glucose dose. ALT, alanine transaminase; AST, aspartate aminotransferase (IU/L)

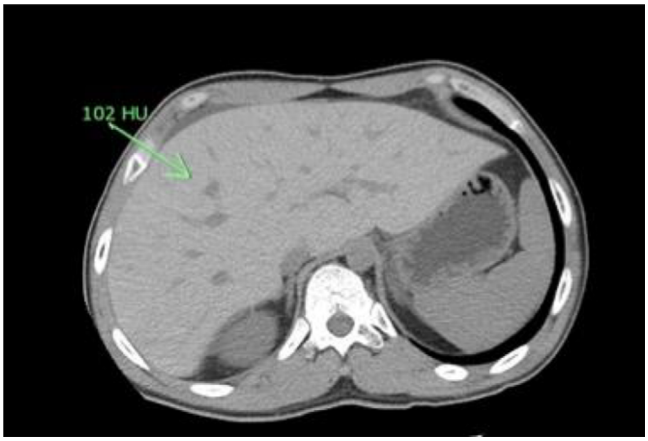

FIGURE 2 A diffuse high absorption area could be confirmed throughout the liver. The arrow indicates an area measuring 102 Hounsfield units (HU), which is higher than normal liver parenchyma (30–60 HU)

and showed a diffusely high absorption (Figure 2). The patient did not undergo a liver biopsy. Based on the clinical episode and because liver function and systemic symptoms subsequently improved by day 8 in the hospital, the patient was moved to a psychiatric ward for management of schizophrenia. Thereafter, his liver function improved to the normal range by day 20. Currently, his glycemia is being controlled by ensuring compliance with insulin therapy and dietician-directed education.

3 | DISCUSSION

The pathological mechanism of glycogenic hepatopathy is accumulation of glycogen in hepatocytes. Insulin and surplus glucose activate glycogen synthase phosphatase conversion to activated glycogen synthase, which is an enzyme needed for glucose-6-phosphate to convert to glycogen, which consequently advances the formation of glycogen and its storage in the liver and obstructs glycogenesis, boosting stores of hepatic glycogen during hyperglycemia (Tsujimoto, 2006).[3] In our patient, sustained release of self-injected insulin from the tissue of the injected site might have further driven glycogen synthesis and inhibited gluconeogenesis and glycogenolysis, leading to boosting hepatocyte glycogen stores. Glycogen overload leads to hepatomegaly.

The symptoms of glycogenic hepatopathy can include abdominal pain and obstructive manifestations such as nausea, early satiety, and vomiting. The usual biochemical results are mildly to moderately high aminotransferases and alkaline phosphatase elevations. The overall prognosis of glycogenic hepatopathy is fair without progression to liver fibrosis. The abnormalities, including hepatomegaly and elevated liver enzymes, are easily reversible with continuous euglycemic control. The other major origin of hepatomegaly in diabetic patients is non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease usually progresses to liver cirrhosis, whereas glycogenic hepatopathy can be reversed by maintenance of better glycemic control, and glycogen deposition does not lead to liver fibrosis.[4] Liver biopsy is still considered the most optimum detection method. Characteristic histological findings are swollen hepatocytes with intracytoplasmic glycogen accumulation in hematoxylin and eosin stain and also abundant glycogen highlighted by periodic acid-Schiff staining.[4] On the other hand, noninvasive imaging modalities such as abdominal ultrasound, magnetic resonance imaging (MRI), and CT help with diagnosis. Either disease indicates bright liver by ultrasound of abdomen. Liver CT shows high density in glycogenic hepatopathy, but low density for non-alcoholic fatty liver disease.[5] MRI typically presents low intensity on T2-weighted images for glycogenic hepatopathy; furthermore gradient-dual echo MRI helps distinguish glycogenic hepatopathy from non-alcoholic fatty liver disease, showing differences in appearance between glycogen deposition and fatty tissue.[2,6] Non-alcoholic fatty liver disease might present low intensity in phase and high intensity out of phase in gradient-dual echo MRI. In our case, neither liver biopsy nor MRI imaging was performed; however, elevated hepatic transaminases, abdominal pain at right hypochondrium to epigastrium with swollen liver, high liver density on CT, poorly controlled blood sugar, and excessive use of long-acting insulin led to the diagnosis of glycogenic hepatopathy.

Poor control of diabetes in schizophrenia may occur due to factors including physical inactivity and poor diet. The relationship between type 1 diabetes mellitus and schizophrenia has been controversial. The prevalence of schizophrenia among patients with type 1 diabetes mellitus is estimated to be between 0.20% and 1.5%.[7] Galler et al[8] published that 0.48% of those with type 1 diabetes up to the age of 25 (median age = 17.0) were being treated with antipsychotic medication, and those receiving antipsychotic drugs had poorer glycemic control and more acute complications compared with those not on antipsychotic drugs. Like the present case, patients with both type 1 diabetes and schizophrenia are an especially vulnerable group at risk for both psychological and somatic issues. Many insulin-treated patients are susceptible to developing hypoglycemia and subsequently visiting the emergency department, so emergency physicians must treat hypoglycemia by infusing glucose as a first-line management to avoid prolonged central nerve system disorder. Hypoglycemia symptoms include cold sweat, the patient feeling cold due to peripheral circulatory disorders, and tachycardia. Our patient was alert with stable vital signs and did not present these subjective symptoms during the follow-up period, although eventually his blood glucose levels dropped lower than 50 mg/dL. Frequent hypoglycemia attenuates the regular sympathoadrenal reaction and adjusts to low plasma glucose level concentration; hypoglycemia-associated autonomic failure in diabetes causes a lack of impaired awareness resulting from this lowering of the hypoglycemic level threshold.[9,10] Physicians might be able to adjust to a lower dose of glucose while monitoring the patient's symptoms.

Insulin self-injection is a good treatment choice for patients with diabetes due to the potential for incremental improvement of metabolic control. Insulin lispro, a rapid-acting human insulin analog, starts to work 15 minutes after subcutaneous injection and lasts about 5 hours. On the other hand, insulin glargine is a long-acting insulin,

lasting over 24 hours with no pronounced peak. Subcutaneous injection of a massive dose in tissue might provide a depot effect, which causes a prolonged outcome by delaying insulin absorption due to local hypoperfusion and mechanical compression. Plasma insulin concentration is supposed to determine the glucose infusion dose, because insulin release from the tissue is unpredictable.[11] Roberge et al[12] reported a maximum glucose deposit rate of 10–11 mg/kg/min. In our case, the maximum dose of glucose administration was 13.3 mg/kg/min. Thus, combined therapy, such as glucagon administration, octreotide administration, and surgical excision of the local insulin injection site, might be able to avoid concentrated glucose infusion.[13] Further, there is the possibility of shortening the treatment duration and consequently possibly stopping glycogenic hepatopathy.

In conclusion, excessive glucose administration for hypoglycemia in the setting of insulin overdose may lead to glycogenic hepatopathy in a patient with uncontrolled diabetes. Emergency physicians should be aware of the common symptoms of glycogenic hepatopathy, such as hepatomegaly and elevated hepatic transaminases.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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