



Liver Cirrhosis and the Hyperglycemic Hyperosmolar Non-Ketotic State

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Diabetic ketoacidosis and the hyperglycemic hyperosmolar non-ketotic state are potentially lethal acute complications of diabetes mellitus. Although well recognized and understood, these syndromes can present in unusual circumstances.

The association between carbohydrate metabolism and chronic liver disease is well established. Sixty to 80% of cirrhotic patients have demonstrable abnormalities of glucose metabolism, with 10–30% of them being overt diabetics [1], yet neither DKA nor a hyperglycemic hyperosmolar non-ketotic state has been described in cirrhotic patients. We present the case of a previously non-diabetic cirrhotic male who developed severe HHNS that resolved without the development of chronic diabetes mellitus.

Patient Description

A 63 year old man with a history of moderate alcohol consumption had been followed at the liver clinic for 4 years prior to admission. He had moderately elevated liver enzymes with normal synthetic liver function and a positive serological test for hepatitis C virus. Present also were a contracted liver, splenomegaly and grade III esophageal varices. There was no evidence of ascites.

Based on the clinical, laboratory and imaging findings, the diagnosis was compensated liver cirrhosis with good synthetic function. He had no other chronic diseases and had abstained from alcohol 10 years earlier. Plasma glucose levels were within normal limits. There was no family history of diabetes mellitus. The only medication the patient received during this 4 year follow-up was propranolol (10 mg three times a day) as a primary prevention of variceal bleeding.

The patient was admitted to the hospital in a state of confusion. He

stopped eating and drinking the day before and became increasingly confused. He had not complained of excessive thirst in the days prior to hospitalization, and had neither changed his routine diet nor increased his intake of carbohydrates. The patient did not exercise routinely.

At admission he was stuporous. His body temperature was 37°C, blood pressure 90/60 mm Hg, and pulse rate 108 beats/minute. His weight was 64 kg without central fat distribution. The heart sounds were normal, the lungs fields were clear and the abdomen was

Table 1. Laboratory data 3 months prior to, during and 6 months after the acute episode of HHNS

Parameter	Prior to admission	At admission	Follow-up (6 months)
Hemoglobin (µg/L)	134	138	128
Hematocrit (%)	42	44	41.5
Leukocytes (10 ⁹ cells/L)	5,200	12,800	3,200
Platelets (L)	84,000	53,000	59,000
Osmolarity (mOsm/L)	280	369	299
Glucose (mmol/L)	4.94	46.52	5.83
Na (mmol/L)	135	154	143
K (mmol/L)	4	5.3	4.3
Blood urea nitrogen (mmol/L)	5.35	15	7.1
Creatinine (µmol/L)	70.7	133	88.4
Total bilirubin (µmol/L)	27.36	58.14	20.52
Albumin (g/L)	38	31	38
Aspartate aminotransferase (IU/L)	125	30	36
Alanine aminotransferase (IU/L)	49	29	29
Hemoglobin A1c (%)			5.8
C-peptide (nmol/L)			1.49
Prothrombin time (sec, INR)	13.8 (1.3)	17.6 (2.3)	15.4 (1.52)

DKA = diabetic ketoacidosis

HHNS = hyperglycemic hyperosmolar non-ketotic state

soft and non-tender. The liver was palpated 3 cm below the costal margin with a span of 12 cm. The spleen was palpated at its edge. There was no evidence of ascites or peripheral edema. Temporal wasting, clubbing, palmar erythema, mild gynecomastia and testicular atrophy were noted. No flapping tremor was elicited.

Results of laboratory tests prior to hospitalization, on admission and at discharge are shown in the Table. The main abnormal findings at admission were severe hyperglycemia, hypernatremia and hyperosmolality. Hypoalbuminemia and coagulation disturbance were also found. Plasma pH was 7.36 and bicarbonate concentration 19 mEq/L. A test for plasma ketones was negative, as were blood and urine cultures.

A diagnosis of HHNS was reached and intravenous fluids and insulin were initiated. During the 24 hours following admission 9 L of NaCl 0.9% and 80 units regular insulin were administered. The patient's condition rapidly improved, and by the third day of hospitalization he was fully awake and hemodynamically stable. Insulin requirements gradually decreased and insulin therapy was discontinued before the patient was discharged from the hospital.

At periodic follow-up visits at the outpatient clinic, fasting and post-prandial plasma glucose and hemoglobin A1c were all within normal limits. Fasting C-peptide, a measure of pancreatic insulin secretion capacity, was in the upper range of normal. An oral glucose tolerance test, performed in accordance with recommendations of the American Diabetes Association, showed plasma glucose levels in a range compatible with impaired glucose tolerance but not diagnostic of overt diabetes mellitus. The test revealed marked hyperinsulinemia (660 pmol/L after 60 min). At a follow-up examination 3 years after the HHNS episode the patient weighed 66 kg. His diet remained unchanged and he reported no episodes of weight loss. He remained normoglycemic – fasting glucose 5.3–6.1 mmol/L (95–110 mg/dl) – and had normal HbA1c values (5.8% and 5.5%).

Comment

To our knowledge this is the first description of a life-threatening episode of HHNS in a patient with liver cirrhosis. The diagnostic criteria for HHNS were met [2]. HHNS is a relatively uncommon life-threatening complication of diabetes mellitus, with 5%–40% of the cases proving fatal [2]. The complication usually occurs in elderly individuals with mild diabetes or unrecognized disease. The pathogenesis of HHNS is multifactorial. Among the factors usually present is a relatively low level of insulin secretion combined with an elevated plasma glucagon level (high glucagon/insulin ratio), which leads to increased glucose production and more significantly to decreased glucose elimination. Osmotic diuresis and severe dehydration are due to the marked hyperglycemia. Moreover, the hyperosmolality suppresses free fatty acid release from adipose tissue and inhibits the pancreatic insulin response to glucose [3,4].

In our patient there was no evident trigger for the development of HHNS at admission. He had well-compensated liver cirrhosis, and his only medication was propranolol. Other than a transient impairment of the liver's synthetic function (decreased albumin and elevated INR) there were no other signs of decompensation of his liver disease. He was normoglycemic before the HHNS episode. Although the plasma glucose level rose to 838 mg/dl (46.5 mmol/L) during the acute episode, it soon returned to the normal fasting range and remained normal throughout the 2 year follow-up. HbA1c was in the normal range throughout follow-up and the oral glucose tolerance test conducted 4 months after hospital discharge did not reveal any gross plasma glucose abnormalities. It did, however, demonstrate a high insulin/glucose ratio compatible with glucose intolerance, which is common in patients with liver cirrhosis.

There was no reason to suspect mild, compensated Type II diabetes mellitus. The patient did not complain of excessive thirst before becoming comatose and was thin without central fat distribution. He

did not exercise on a routine basis and his diet remained unchanged after discharge from the hospital.

Several mechanisms may be involved in the development of impaired glucose metabolism in cirrhotic patients regardless of the etiology of their liver disease. There is a decreased first-pass insulin effect [3] due to intrahepatic porto-caval shunts, which leads to relative hypoinsulinemia. The hyperglucagonemia, caused by porto-systemic shunting, stimulates gluconeogenesis. Concomitant hypoinsulinemia and hyperglucagonemia lead to increased hepatic glucose output. Petrides et al. [4], using glucose and insulin clamps, reported a decrease in peripheral (muscular) glucose uptake and glycogen formation in cirrhotic patients.

Although propranolol has been associated with HHNS [2], we do not believe it was implicated in our patient since he had been taking a small dose for at least 3 years prior to admission and continued to do so throughout the follow-up period without any adverse effects.

The patient was infected with the hepatitis C virus. Mason et al. [5] reported that glucose intolerance is more prevalent in HCV patients than in patients with non-HCV liver disease, as is overt diabetes mellitus which has a prevalence rate of 39%–50% [5]. These investigators concluded that HCV infection is a more important predictor of glucose intolerance than cirrhosis, and the coexistence of these factors increases the risk of diabetes, especially in patients with genotype 2a which is preferentially associated with extra-hepatic syndromes. We believe that infection with HCV contributed to the development of HHNS in our patient.

Although the patient's diabetes did not meet the criteria of the ADA or World Health Organization, the acute episode of HHNS may have stemmed from a minor impairment of glucose metabolism. Since we did not find any association between HHNS and normal or impaired glucose tolerance in the medical literature, we presume that this is the first description of a case of HHNS

ADA = American Diabetes Association

in a non-diabetic patient. Liver cirrhosis, impaired glucose tolerance and diabetes mellitus are common disorders with overlapping pathophysiologic mechanisms. It is surprising that HHNS has not been described previously in patients with liver cirrhosis.

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