Brief Report

Profound Ambulatory Hypoglycemia: A Rare Entity

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A 49-year-old man with a history of hepatocellular carcinoma, alcohol abuse, and insulin-dependent diabetes mellitus was noted to be completely asymptomatic despite a plasma glucose level of 4 mg/dL. The possible pathophysiology of this unusual occurrence of "hypoglycemia unawareness" is discussed.

Key words. Hypoglycemia; adaptation, physiological; carcinoma, hepatocellular; diabetes mellitus, insulin-dependent.

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The central nervous system manifestations of hypoglycemia vary in presentation and range of severity from altered mental status to seizures. In addition, a small proportion of patients with insulin-dependent diabetes mellitus (IDDM) have decreased or absent hypoglycemic awareness. Conditions that may induce hypoglycemia include administration of exogenous insulin, excessive endogenous insulin production (as in insulinomas), drugs, hepatic and renal diseases, sepsis, and malnutrition.[1]

The case described below serves as an important reminder that hypoglycemia may be asymptomatic and can be missed if not considered. We report what we believe is the first case in the literature of such profound hypoglycemia (4 mg/dL) in an asymptomatic ambulatory patient.

Case Report

A 49-year-old man was admitted to the hospital with a history of hepatocellular carcinoma, chronic pancreatitis, IDDM, and alcohol abuse. At the time of admission, he was receiving 25 units of NPH human insulin daily, as well as oxycodone, hydroxyzine, and furosemide.

The patient had a history of chronic alcohol abuse, which had resulted in chronic pancreatitis and IDDM. The patient lived with his family, who were responsible for his care and administration of his medications. On a routine visit to the ambulatory clinic, his family reported that he had been confused and weak for the past 3 days.

Physical examination at the time of admission revealed a thin, emaciated, malnourished, icteric man who was alert and oriented to time, place, and person. He followed commands well and answered questions appropriately. His speech was clear. Physical examination findings were within normal limits except for ascites and pitting edema of the lower extremities.

Laboratory studies revealed a leukocyte count of 10.3×10^9/L with a mild left shift. His hemoglobin level was 8.5 g/dL. The PT and PTT were prolonged. Results of his liver function tests were as follows: total protein 6.9 g/dL; albumin 1.8 g/dL; total bilirubin 3.0 mg/dL; alkaline phosphatase 148 U/L; LDH 302 U/L; and AST 99 U/L. These results had not changed significantly from those obtained during his previous admission a few weeks before. Serum and urine were negative for ketones. A routine fingerstick determination of blood glucose level was reported by the nurse to be zero. Because of the low results, a plasma blood glucose test was done. To our astonishment the patient's glucose level was reported as 4 mg/dL. The test was immediately repeated and the previous results were confirmed. Plasma insulin, C-peptide, and glucagon levels were not determined, as it was believed that the profound level of the patient's hypoglycemia was a result of the insulin that had been administered by a family member a few hours before

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Table 1. Causes of Hypoglycemia

Conditions Associated with Overutilization of Glucose	Conditions Associated with Underproduction of Glucose
Hyperinsulinism	Hormone deficiencies
Insulinoma	Hypopituitarism
Sulfonyl urea, exogenous insulin	Adrenal insufficiency
Autoimmune disease	Catecholamine insufficiency
Drugs (eg, quinine, pentamidine)	Glucagon deficiency
Endotoxin shock	
	Enzyme defects
Appropriate insulin level	Glucose-6-phosphatase
Cachexia with fat depletion	Pyruvate carboxylase
Extrapancreatic tumors	Fructose 1,6-diphosphatase
Carnitine deficiency	
	Substrate deficiency
	Malnutriton
	Late pregnancy
	Liver disease
	Drugs
	Alcohol
	Propranolol
	Salicylate

Adapted from Foster and Rubenstein.[3]

admission. Results of blood and urine cultures and findings on chest radiographs taken at the time of admission were normal.

The patient was immediately given 50 mL of 50% dextrose water intravenously, and within 2 hours, his blood glucose level rose to 45 mg/dL. The hypoglycemia resolved without any discernible change in his mental status.

The patient was discharged a few days later with instructions not to take insulin. Blood glucose levels before discharge were consistently over 150 mg/dL. The patient died at home a few weeks later of unknown causes. No autopsy was performed.

Discussion

Hypoglycemia is defined as the occurrence of a wide variety of symptoms in association with plasma glucose levels of 40 mg/dL or less.[2] Diabetes mellitus, alcoholism, and sepsis, alone or in combination, account for 90% of hospital admissions.[1,3] In fact, type II diabetics treated with insulin have a 40% incidence of hypoglycemic episodes.[4] A list of the many causes of hypoglycemia is given in Table 1.

The diagnosis of hypoglycemia should be considered in patients presenting with adrenergic or neuroglycopenic symptoms and signs (Table 2).[5,6] Although the clinical features are helpful in making the diagnosis, a significant proportion of these patients either are asymptomatic or have only altered mental status when examined. The patient's initial symptoms of strange behavior

Table 2. Adrenergic and Neuroglycopenic Symptoms of Hypoglycemia

Autonomic Nervous System Dysfunction	Central Nervous System Dysfunction
Sweating	Diplopia
Shakiness	Blurred vision
Anxiety	Confusion
Palpitations	Abnormal behavior
Weakness	Amnesia
	Unconsiousness
	Seizures

From Service FJ. Hypoglycemic disorders. In: Wyngaarden JB, Smith HL, Bennett JC, eds. Cecil's textbook of medicine. Philadelphia: WB Saunders, 1992:1313. Reprinted with permission by WB Saunders.

and confusion before being seen by us were probably a result of fluctuations in his plasma glucose levels resulting from unscheduled meals and irregular insulin administration. The absence of clinical symptoms when examined probably reflected a variation in his plasma glucose level.

Clinical manifestations of hypoglycemia range from subtle impairment of mentation to coma and death. Between these extremes, a variety of different expressions occur, including visual symptoms, confusion, lethargy, behavioral changes, impairment of performance of routine tasks, vertigo, paresthesia, and focal neurological signs and seizures.[7] At least 23% of patients with IDDM, however, have partial or complete hypoglycemic unawareness.[7] This reduced level of awareness is thought to be associated with a reduced plasma epinephrine response,[8] which may be an important determinant for the wide variability of symptoms among patients with similar blood glucose levels and mechanisms of hypoglycemia.[1] In addition, autonomic neuropathy associated with longstanding diabetes and impaired glucagon secretion could lead to central nervous system adaptation by reducing both the symptoms of and defenses against developing hypoglycemia leading to recurrent severe hypoglycemia, thus creating a vicious cycle.[9]

In their study of 125 patients with hypoglycemia, Malouf et al[1] found no correlation between blood glucose levels and symptoms. The average blood glucose level was between 12 and 40 mg/dL, with a large proportion of these patients brought to the emergency department in a coma or near-comatose state. In patients with cancer, blood glucose levels as low as 2 mg/dL have been reported, with the patients in a coma.[1] The hypoglycemia that occurs in cancer patients is thought to be related to impaired gluconeogenesis, decreased glucose output by the liver, and excessive glucose utilization by the neoplasm.[10] In addition, this patient was clinically malnourished, and this also probably contributed to the hypoglycemia. A combination of reduced carbohydrate intake and hypoalbuminemia are clinical predictors of hypoglycemia in diabetic patients.[11]

Alcohol in itself does not appear to cause a higher incidence of hypoglycemia when compared with a population without elevated ethanol levels as reported by Spore et al.[12] When consumed by a patient with malnutrition and hepatocellular cancer, however, alcohol could induce hypoglycemia. All these mechanisms probably were operational in the patient discussed in this report. In the majority of reported studies, coma occurred at levels of 2 to 28 mg/dL, while stupor occurred in the range of 8 to 59 mg/dL and obtundation at 9 to 60 mg/dL. Neither duration of hypoglycemia nor accompanying illness explained the overlapping of these ranges in the studies.[13]

Alcohol induces hypoglycemia by inhibiting gluconeogenesis[14,15] as it depletes hepatic nicotinamide adenine dinucleotide (NAD), a cofactor that is necessary for the entry of most precursors into the gluconeogenic pathway. It does not inhibit glycogenolysis. Ethanol also inhibits cortisol and growth hormone responses to hypoglycemia.[15–17] In addition, epinephrine responses are delayed as well.[18] Glucagon release appears to be normal, although delayed responses have been reported.[18] Therefore, in diabetics with prolonged hypoglycemia in which gluconeogenesis is the dominant source of hepatic glucose production, ethanol can contribute to the progression and severity of hypoglycemia.

The case reported herein demonstrates that a profoundly hypoglycemic patient can nonetheless be awake and oriented, and able to respond, speak, and communicate, despite blood glucose levels that are near the lower limit of detection. In their study of the effects of mild hypoglycemia on cognitive functioning in diabetic children, Ryan et al[19] found that there is a high degree of subject variability and that, in addition to plasma glucose values, unknown physiological variables are also responsible for triggering cognitive impairment in these patients. It is also likely that the hypoglycemia warning symptoms are unrelated to the type of insulin (ie, human or animal).[20]

We speculate that this patient's profound hypoglycemia was present for an extended period owing to his underlying disease, and the lack of altered sensorium was the result of a remarkable physiological adaptation of the brain to hypoglycemia.

Despite extensive literature reviews, we did not find any other report of such an unusual clinical presentation of hypoglycemia with altered sensorium.

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