A Case of Diabetic Non-Ketotic Hyperosmolar Coma with an Increase with Plasma 3-Hydroxybutyrate

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Abstract. We have seen a case of "diabetic non-ketotic hyperosmolar coma" with ketosis. An 84-year-old man was brought into the hospital in a deeply comatous and dehydrated state. The initial blood glucose level was 1252 mg/dl with plasma osmolarity of 435 mOsm/l, but no ketonuria was detected by the nitroprusside method (Ketostix). However, the plasma 3-hydroxybutyrate (3-OHBA) level was 5 mM in a newly developed bedside film test. The serum ketone bodies were later found to be 5.56 and 0.82 mmol/l for 3-OHBA and acetoacetate (AcAc), respectively. A marked increase in glucagon, cortisol and ADH with renal dysfunction (creatinine 5.0 mg/dl) were noted. An abnormal electrocardiogram, occular convergence and chorea like movement disappeared after correction of metabolic disturbances. The moderate level of IRI (14 μU/ml) on admission and a good response to glucagon 2 months after admission also indicate that the present case is a typical hyperosmolar non-ketotic coma. Because of a preferential increase in 3-OHBA, ketonuria seemed to be absent in the regular nitroprusside test. Marked dehydration is thought to cause renal dysfunction, and the increase in ADH may have helped to prevent further aggravation of ketoacidosis. We propose to change the term hyperosmolar nonketotic coma (HNC) to diabetic hyperosmolar coma (DHC), because sometimes patients with hyperosmolar non-ketotic diabetic coma are ketotic, as seen in the present case. Determination of 3-OHBA or individual ketone bodies in blood is important and essential for the differential diagnosis of diabetic coma. The diagnosis of either ketoadidotic or hyperosmolar coma should be made depending on the major expression of ketoacidosis or hyperglycemic hyperosmolarity.

Key words: Hyperosmolar diabetic coma, Ketoacidosis, Ketogenesis, ADH, C-kinase.

THE HYPERGLYCEMIC hyperosmolar non-ketotic coma is characterized by severe hyperglycemia, hyperosmolarity and dehydration in the absence of ketoacidosis [1–7]. But recently we have seen a case of hyperglycemic hyperosmolar coma with significant ketosis and acidosis. The clinical background and features of ketoacidosis and hyperosmolar nonketotic coma are quite different. The former is characterized by acute onset in insulin dependent diabetes mellitus (IDDM) in young patients and proceeds to permanent diabetes after a remission period. The latter occurs in aged non-insulin dependent diabetes mellitus (NIDDM) patients with frequent association of reversible renal dysfunction and usually pancreatic beta cell function is maintained. In the present case, in spite of the presence of ketoacidosis, the overall clinical features were regarded as those of

Received: July 2, 1990
Accepted: August 6, 1991
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the latter type because of the onset of marked hyperglycemia, dehydration and uremia in NIDDM with subsequent recovery of pancreatic beta cell function.

Subject and Clinical Course

An 84-year-old man was brought into our clinic in an obtunded state. A diagnosis of diabetes mellitus had been made at the age of 59. He had been treated with diet alone or on occasion with oral hypoglycemic agents. He had experienced polydipsia and polyuria 2 weeks before. On week prior to admission he could not eat enough because of soreness around the mouth due to stomatitis. About three days before admission, he had been drowsy, and in the morning of admission he was found in a confused state in bed, difficult to arouse, and became unconscious by the time of his admission.

He was slightly overweight (Height; 145.5 cm, Body Weight; 48.5 kg) and respiration was deep with a rate of 20/min, but no acetone odor was noted. The systolic blood pressure was low (60 mmHg), and the heart rate was 72 per min. The skin turgor had markedly decreased. The neck veins were not visible. There was a grade I precordial systolic murmur. The lung sound was clear. There was conjugate deviation of the eye to the right. Ankle reflex was absent, and pain sensation in the lower extremities was markedly decreased, indicating the presence of diabetic neuropathy.

Laboratory Findings (Table 1)

The following values were abnormally increased: hematocrit 58.9%, white blood cell count 2280/mm³, blood glucose 1252 mg/dl, BUN 175 mg/dl and serum creatinine 5.0 mg/dl. Electrolyte values, sodium (143 mEq/l) and chloride (93 mEq/l) were normal, but an increase in potassium (7.4 mEq) and a decrease in bicarbonate (11.7 mEq/l) were noted. The arterial blood pH was 7.25, PCO₂ was 27.6 mmHg with a base excess of −14.1 mEq/l. The anion gap was 38.3 mEq/l. Urinary glucose was markedly positive, but urinary ketone test with the nitroprusside method (Ketostix) was negative. The plasma level of 3-OHBA in bedside film test was 5.0 mM on admission and was later found to be 5.6 mM/l with 0.8 mM/l AcAc in a direct enzymatic assay. The clinical course of the patient is depicted in Figs. 1 and 2. After the continuous infusion of a small dose (4–10 U/h) of intravenous insulin and 5 liters of saline, blood glucose and ketone bodies steadily decreased and fell below 20% of the basal value at 12 h. Consciousness was gradually restored 24 h later.

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<th>Table 1. Laboratory data</th>
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HYPEROSMOLAR COMA

Fig. 1. Effect of insulin and fluid therapy for a patient with hyperosmolar diabetic coma. ADH: antidiuretic hormone, BE: base excess, Cr: creatinine, GH: growth hormone, IRG: Immuno reactive glucagon (P: pancreatic, T: total), IRI: immunoreactive insulin, 3-OHBA: 3-hydroxybutyric acid.

after admission. An inverted T wave in the ECG observed on admission and which became prominent during the initial fluid and insulin therapy subsequently normalized during a course of metabolic correction. In addition, chorea-like movements in the right leg which were induced during hyperosmolar coma disappeared during tiapride administration days 40-50. MRI of the brain exhibited multiple cerebral infarction. Insulin sensitivity for glucose utilization assessed by the SSPG (steady state plasma glucose) method was normal (106 mg/dl, Fig. 3). Plasma levels of ketone bodies were well suppressed 2 h after the insulin infusion, indicating normal insulin sensitivity in adipose tissue as well as in the liver. The effect of the combined intravenous glucagon (1 mg) and glucose on insulin secretion was normal during the 50 day period of the admission.

Discussion

The diabetic “non-ketotic” hyperosmolar coma often observed in patients with NIDDM has been characterized by extreme hyperosmolar hyperglycemia without ketoacidosis. As a result of the marked degree of hyperglycemia and glycosuria, patients became severely dehydrated with a great loss of glucose, sodium and water in urine. The progressing dehydration leads to deteriorated renal function, reducing the capacity of the kidney to excrete glucose and further aggravating the hyperglycemic state. The reason for the absence of significant ketosis in this syndrome has been speculated by many investigators. Joffe and associates suggested that the lack of ketosis may be explained by the metabolism of incoming free fatty acid along non-ketogenic pathways (esterification) in the liver [8]. Gerich et al. reported that dehydration and hyperosmolarity themselves suppress lipolysis, thus contributing to the non-ketotic
Fig. 2. Clinical course of a patient with hyperosmolar diabetic coma. FPG: fasting plasma glucose.

Fig. 3. Insulin sensitivity test. Glucose (12% solution, 6 mg/kg/min), monocomponent act-rapid human insulin (0.77 mU/kg/min), and somatostatin (250 µg/h) were infused for 2 h through an antecubital vein via a constant infusion pump. Steady state plasma glucose (SSPG) levels at 2 h were measured.
Recently Kojima et al. reported that vasopressin suppresses glucagon or epinephrine-stimulated ketogenesis through activation of c-kinase in isolated hepatocytes [10]. Harano et al. proposed that blood vasopressin which is known to have a hyperglycemic effect and is high in the dehydrated hyperosmolar state plays a suppressive role in hepatic ketogenesis. Therefore, suppression of ketogenesis while enhancing hyperglycemia by vasopressin may be an important factor in the pathophysiology of hyperglycemic hyperosmolar coma [11]. In fact, the initial vasopressin level in the blood was greatly increased (58 pg/ml) in our patient, but failed to suppress ketoacidosis. Without this increase, severer ketoacidosis may have developed. Vasopressin alone cannot explain the mechanism, but it should be considered as one of the regulatory hormones in the pathophysiology of non-ketotic diabetic coma. Glucagon is known to stimulate hepatic ketogenesis [12, 13]. In the present case, pancreatic glucagon was markedly increased (720 pg/ml). The mechanism of a further increase in pancreatic glucagon to 1600 pg/ml and the disappearance of gut glucagon after insulin and fluid therapy remain to be elucidated.

Halperin et al. reported recently that ketosis is an inevitable consequence of the hyperglycemic hyperosmolar syndrome and the increased 3-OHBA is thought to facilitate its metabolism in the central nervous system [14]. In fact, analysis of over 1000 cases of acutely decompensated diabetes mellitus at Gray Memorial Hospital from mid-1973 to mid-1975 revealed that about 67% of the patients had mild or moderate ketoacidosis and about 25% had severe ketoacidosis (HCO₃₃ < 10 mEq/l, serum osmolarity > 350 mOsm/l). Two percent had a pure hyperglycemic hyperosmolar state (serum osmolarity > 350 mOsm/l without ketonemia or ketonuria), and 1% had almost pure severe diabetic ketoacidosis (HCO₃₃ < 10 mEq/l, glucose > 150 mg/dl) [15]. Therefore, it is postulated that most of the patients with “non-ketotic” hyperosmolar coma were at least ketonemic when ketone bodies were properly determined. In fact, we had seen a similar case, a 66-year-old female with hyperglycemia (587 mg/dl) and hyperosmolarity (403 mOsm/l) but without ketonuria; but her blood 3-OHBA was 1.6 mmol/l with a slight increase in AcAc (0.85 mmol/l), indicating the presence of ketosis in hyperosmolar coma. Altogether we saw 7 so-called non-ketotic hyperosmolar diabetic coma cases. They all exhibited mild or non-ketouria (2 subjects: +, 2; ±, 3: −). Five out of six in whom ketone bodies were determined had ketosis exceeding total ketone bodies more than 1 mM (3-OHBA/AcAc =1.4 to 7), indicating that mild ketonemia is a rather common finding in hyperosmolar diabetic coma. The present case is an extreme case of this syndrome who exhibited no ketonuria but had a total ketone body level of 6.4 mM with a high ratio of 3-OHBA/AcAc (=7).

Among ketone bodies, AcAc reacts with nitroprusside reagent (Ketostix), but 3-OHBA failed to react with this reagent at all. In our patient, a prominent increase in the 3-OHBA/AcAc ratio caused a negative nitroprusside reaction in the urine and blood. Since our patient had a marked decrease in the extracellular fluid volume and deteriorated into a state of so-called hypovolemic shock, an adequate supply of oxygen could not be delivered to tissues, resulting in a preponderant increase in 3-OHBA over AcAc. The equilibrium between AcAc and 3-OHBA is determined in large part by the ratio of reduced and oxidized NAD in mithochondria. Hypoxia with an increased level of NADH is thought to drive the reaction toward 3-OHBA [16].

The pathogenic spectrum of acutely decompensated diabetes mellitus ranges from pure hyperosmolar hyperglycemia without ketosis, to mixed hyperosmolar hyperglycemia and ketosis or ketoacidosis and to almost pure ketoacidosis without significant hyperosmolar hyperglycemia [17]. Nevertheless, until recently, detection of a clinical increase in ketosis tends to depend on the nitroprusside test in most of the diabetes clinics. A bedside film test and direct enzymatic assay method for 3-OHBA or individual ketone bodies are now available and essential for the diagnosis of ketogenic or non-ketotic diabetic coma [18, 19]. An increase in 3-OHBA is possibly a rather common finding in hyperosmolar coma. Therefore, we propose that the term “hyperosmolar nonketotic coma (HNC)” should be changed to “diabetic hyperosmolar coma (DHC)".
References