Hyperosmolar Hyperglycemic Nonketotic Coma (HHNC) Accompanied with Acute Renal Failure, Rhabdomyolysis and Acute Obstructive Hydrocephalus

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Introduction

Hyperosmolar hyperglycemic nonketotic coma (HHNC) was first recognized by Sament and Schwarz1) in 1957. It is characterized by hyperglycemia, hyperosmolarity, hypernatremia, and depression of the sensorium without the presence of ketoacidosis. Complications associated with HHNC include metabolic disturbance, rhabdomyolysis and renal failure, cardiovascular, thromboembolic and neurological disorders2-13. We report herein a case with the very rare complication combined with renal failure, rhabdomyolysis and acute obstructive hydrocephalus in the clinical course of HHNC.

Case Report

A 65-year-old female was admitted to a regional hospital due to ileus in connection with total hysterectomy performed 14 years ago. She was treated conservatively by total parental nutrition (TPN). Nine days later she underwent resection of the intestine due to adhesion ileus. Infusion toward TPN was resumed as scheduled. The blood sugar level exceeded over 500 mg/dl on the following day of the operation. Suitable volume of lactated Ringer's solution was administered for polyuria. Insulin was not administered at that time. On the 4th postoperative day she developed restlessness and stupor. She was treated as hyperosmolar hyperglycemic nonketotic coma (HHNC) due to raised blood sugar (over 500 mg/dl), sodium was 190 mEq/l while chloride was 138 mEq/l. Two liters half saline was administered within 6 hrs and 32 units of regular insulin by percutaneous injection and 10 units of regular insulin were administered by intravenous injection. Her systolic blood pressure dropped toward 60 to 70 mmHg systolic pressure and she was given dopamine of 10 μg/kg per min. Immediately after this episode, she was referred to our intensive care unit (ICU) owing to coma and hypotension. Her conscious level was GCS of 5. Her laboratory data on admission to ICU were: red blood cell (RBC) count 312 ×10⁴/mm³, hemoglobin 9.4 g/dl, hematocrit 30.6%, platelets 19,000/mm³, white blood cell (WBC) count 14,900/mm³, plasma osmolarity 431 mOsm/l, urine osmolarity 457 mOsm/l, urine ketone body negative, blood sugar 414 mg/dl, blood urea nitrogen (BUN) 75 mg/dl, sodium 181 mEq/l, potassium 4.7 mEq/l, chloride 145 mEq/l, arterial blood gas analysis (F₁O₂ 1.0) pH 7.470, PaO₂ 128 mm Hg, PaCO₂ 32 mm Hg, HCO₃⁻ 23 mmol/l, base excess (BE) -0.6 mEq/l and saturation of arterial blood 98.9%. Subsequent laboratory results were: aspartate aminotransferase (AST) 113 IU/l, alanine aminotransferase (ALT) 53 IU/l, alkaline phosphatase (ALP) 45 IU/l, γ-glutamyltranspeptidase (γ-GTP) 45 IU/l, lactate dehydrogenase (LDH) 1,168 IU/l, creatine phosphokinase (CPK) 18,390 IU/l, amylase (AMY) 265 IU/l, total protein (TP) 5.0 g/dl, creatinine 1.1 mg/dl, serum myoglobin 36,988.5 ng/l and urine myoglobin 224,553.0 ng/l.

She was treated with intratracheal intubation and assisted ventilation and also administered dopamine between 3 and 5 μg/kg per min, 10-15 units of regular insulin per hour for the initial 14 hrs and eight liters half saline with potassium supplement within 20 hrs. Her central venous pressure was maintained at between 6 and 10 mmHg. On the first hospital day, to negate the infectious focus in the lower
abdomen following the operation as soon as possible, exploratory laparotomy was performed in the ICU owing to hemodynamically unstable state and the patient was on assisted ventilation. After the initial treatment, insulin administration was reduced from 0.5 to 1.0 unit per hour. As shown in Fig. 1, continuous hemodiafiltration (CHDF) was introduced intermittently due to oliguria. A hemofilter of Panflo-1.0 was used. A protease inhibitor, nafamostat mesilate was administered as anticoagulant in the dose of 30~50 mg/h. Sterile bicarbonate dialysate was used with the flow rate of 1,000 ml/h. Filtration rate was approximately 400 ml/h. For replacement fluid, half saline was used at the rate of 300~500 ml/h. Fluid balance in dialyser was plus 385 ml on the 1st day, plus 740 ml on the 2nd day,
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Fig. 2. CT scans on the 10th hospital day show a bilaterally marked dilatation of cerebral ventricles with a marked periventricular low density and no visualization of peripontine cistern due to brain stem low density with evidence of brain stem edema.

plus 1,870 ml on the 3rd day, 0 ml on the 4th day. Thrombocytopenia and elevation of fibrin split products which indicates disseminated intravascular coagulation (DIC) was treated with a total of 50 units of platelets and protease inhibitor. CHDF was stopped on the day 6, because urine output was over 100 ml/h and hemodynamically stable condition was maintained with low dose dopamine. During these treatments, she fell into a deep coma and almost stopped spontaneous respiration on the 10th hospital day. The pupils were equal, dilated and almost did not react to light. The score of GCS was 3. As shown in Fig. 2, CT scans indicated a marked dilatation of cerebral lateral ventricles with marked periventricular low density and no visualization of peripontine cistern with evidence of brain stem edema. She underwent an emergency ventricular drainage. The increase in blood sugar after the 10th hospital day was due to the administration of glucocorticoids to treat brain edema. Creatinine clearance of the patient gradually recovered. TPN was not introduced until the 19th hospital day. Her level of consciousness gradually recovered and her CT scans on the 46th hospital day showed marked dilatation of IIIrd and IVth ventricles, basal cisterns and cerebral sulci with evidence of brain stem and cerebral atrophy as shown in Fig. 3. After these treatments, she gradually recovered and subsequently she was transferred to a general ward with a score of GCS 13.
Discussion

Nonketotic hyperosmolar diabetic coma, mainly develops in the elderly, is characterized by raised blood sugar, increased plasma osmolarity, raised plasma sodium, and depression of the sensorium in the absence of ketosis. The reported mortality of HHNC ranges from 10% to 60%, but a chronological review of reported cases reveals two eras of HHNC mortality. Data from the 1960s and 1970s are associated with higher mortality rates, and those in the last 15 years with mortality between 10% and 17%. Most deaths, however, are not directly due to the presence of HHNC, but rather due to such associated medical conditions like severe metabolic disturbances, renal failure due to rhabdomyolysis, cardiovascular, thromboembolic, and neurological events. Several mechanisms have been postulated.

Our case had acute renal failure, rhabdomyolysis and acute obstructive hydrocephalus due to brain stem edema.

Rhabdomyolysis is rarely caused by diabetic ketoacidosis and even less commonly experienced in hyperosmolar nonketotic coma.

Nevertheless, a recent study suggests that rhabdomyolysis is a common finding in hyperosmolar states. Singhal et al. reported that sixteen of 31 patients with hyperosmolar state related to diabetic ketoacidosis or hyperosmolar coma showed bio-

Fig. 3. CT scans on the 46th hospital day show a marked dilatation of 3rd and 4th ventricles and moderately dilatated cerebral basal cistern and sulci with evidence of brain stem and cerebral atrophy.
chemical evidence of rhabdomyolysis. The exact pathological mechanism by which hyperosmolarity causes rhabdomyolysis is not known. It has been postulated that the hyperosmolarity may cause shrinkage of the muscle cells and impair the utilization of glucose, thus resulting in the altered cell wall integrity. The frequent coexistence of hypernatremia with hyperosmolarity, masking hypokalemia, may also play a role in the pathogenesis. Serum CPK level, however, does provide a sensitive test for rhabdomyolysis in these patients with acute renal failure associated with hyperosmolar nonketotic coma. All similar cases reported in the literature have a marked increase in the plasma CPK, ranging from 9,250 IU/l to 483,000 IU/l. Rhabdomyolysis is diagnosed in the presence of myoglobinuria and raised levels of serum CPK. Although these sometimes occur with tender swelling of muscles, this is not universal. Nontraumatic causes are well recognized and myoglobinuria secondary to rhabdomyolysis is an accepted cause of acute renal failure, as occurred in the patient we described.

Myoglobin has a molecular weight of 16,800. The CHDF may have helped in removing myoglobin from the blood resulting in improved patient’s prognosis. Acute renal failure associated with rhabdomyolysis due to hyperosmolar nonketotic coma is uncommon. However, caution in interpretation is needed as rhabdomyolysis in these patients are often asymptomatic. Early diagnosis and appropriate management of rhabdomyolysis will reduce the morbidity and mortality. The best screening test available is serum CPK level as the urine examination for myoglobin is often negative. Continuous hemofiltration (CHF) or hemodiafiltration (CHDF) is the recommended dialysis therapy when the renal failure is complicated by hyperosmolarity and hypernatremia. This is especially useful for hemodynamically unstable patients in the ICU who would not tolerate rapid removal of fluid. We introduced CHDF during these treatments due to oliguria and maintained the hemodynamically stable condition by monitoring therapy. In HHNC associated with rhabdomyolysis and acute renal failure CHDF would allow: (1) a slow and constant decrease in serum osmolarity eventually avoiding the development of brain edema and (2) the elimination of myoglobin in the ultrafiltrate fluid which could result in a shorter duration of acute renal failure.

In laboratory animals or patients with diabetic coma, when the plasma glucose is rapidly lowered, the decline in CSF glucose lags behind that of plasma. It has been suggested that the slower fall in CSF glucose may reflect a similar decline in brain glucose, thus resulting in an osmotic gradient from brain to plasma, with a resultant movement of water into the brain. A rapid decline of glucose in the plasma might be expected to induce an osmotic gradient between plasma and brain if either glucose or another osmotically active substances were retained in brain tissue water such that the rate of decline in brain did not parallel that in blood. Since it has been shown in several published cases that the CSF glucose concentration is considerably lower than the blood glucose concentration, the CSF sodium concentration ought to exceed the serum sodium concentration. This CSF sodium excess should be osmotically equal to the CSF glucose deficits in regard to the serum, i.e. for each 18mg% of difference in glucose concentration, there should be 0.5mEq/l of sodium excess in CSF. As treatment is initiated, rehydration and sodium replacement should parallel reduction of the hyperglycemia. The rapid correction or over correction of hypernatremia is believed by many to be the crucial factor in the causation of central pontine myelinolysis (CPM).

This rapid fall of serum osmolarity may well have resulted in a rebound phenomenon that causes cerebral edema. When nonketotic coma was diagnosed, there was osmotic equilibrium between plasma and cerebrospinal fluid although the respective constituents were different. Glucose was significantly higher in plasma while sodium and its anions were significantly higher in cerebrospinal fluids. Fujioka et al. postulated that plasma hyperosmolarity, which results mainly from hyperglycemia and hypernatremia, induces endothelium damage that leads to brain-stem edema, followed by the obstruction of the aqueduct and fourth ventricle. The fact that hyperosmotic insult predominantly affected the brain stem in this case may be explained by the theories of Norenberg and McKee et al. who suggested a strong association between the genesis of CPM and osmotic injury to the endothelium. It is also possible that a structural abnormality, such as aqueduct stenosis, in the brain-stem ventricular drainage system might predispose the patient to the development of obstructive hydrocephalus following only slight cerebral swelling.

The greatest danger to the patient with HHNC is hypovolemia with progressive shock or thromboembolism; rapid volume restoration is essential to
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patient’s survival. The second stage of treatment, usually beginning 12 to 24 hrs after initiation of therapy, includes treatment of the precipitating illness, restoration of tonicity, correction of acid-base imbalance, and initial electrolyte restoration. Full restoration of electrolyte, magnesium, and phosphate deficits, the third stage of treatment, may take 1 to 2 weeks.

In our case, the patient was maintained on low dose dopamine, and fluid imbalance corrected with half saline and potassium supplement with 10-15 units of insulin, and maintaining the central venous pressure between 6 and 10 mmHg using CHDF (monitoring therapy). To restore hypovolemia and electrolyte disturbance, filtration rate was set at around 400ml/h rather than 200ml/h as in usual case. Therefore, we could use enough half saline as replacement fluid at 300-500 ml/h. The initial treatment was successful in treating acute renal failure using CHDF even with hypovolemic shock. However, the patient developed acute obstructive hydrocephalus. It was decided that we terminated CHDF on the 6th hospital day which had started on day 2. We stopped CHDF because enough volume of urine and hemodynamically stable state were achieved. This cessation resulted in an increase of BUN up to 112 mg/l and a small increase in plasma osmolarity of 339 mOsm/l; this could have resulted in a serious osmotic insult to the brain stem edema, thus causing acute obstructive hydrocephalus leading to brain stem edema after recovering from hypovolemic shock. It is important to maintain a stable condition in serum osmolarity and fluid balance in critically ill patients at risk from developing brain edema. Our experience shows that even in a delayed treated case, with skillful ICU management and appropriate treatment like ventricular drainage could be successful in treating the patient although it had progressed to shock, acute renal failure and obstructive hydrocephalus.

References

ABSTRACT

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A 65 year-old female was admitted to a regional hospital with a complaint of ileus following a total hysterectomy performed 14 years ago. She was treated conservatively by total parental nutrition (TPN). Nine days later she underwent resection of the intestine due to rebound tenderness in the lower abdomen. Infusion toward TPN was resumed the following day after the operation. On the 4th postoperative day she developed restlessness and stupor. She was treated as a hyperosmolar hyperglycemic nonketotic coma (HHNC). She was referred to our intensive care unit (ICU) due to coma and hypotension. Her conscious level was a score of 5 on the Glasgow Coma Scale (GCS). Continuous hemodiafiltration (CHDF) was introduced intermittently due to oliguria. During these treatments, she fell into a deep coma and almost stopped spontaneous respiration on the 10th hospital day. CT scans showed a marked brain stem edema and acute obstructive hydrocephalus. She underwent an emergency ventricular drainage. After these treatments, her consciousness level gradually recovered and subsequently she was transferred to the general ward with a score of 13 on the GCS. Although she had serious complication of renal failure, rhabdomyolysis and also hydrocephalus in this case, she was recovered in intensive care. It is advisable to maintain the patients on clinical parameters (monitoring therapy) using CHDF.

Received for publication on June 8, 1999 (99-036)