REPORT ON TWO CASES OF HYPEROSMOLAR, HYPERGLYCAEMIC NONKETOTIC DIABETIC COMA

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INTRODUCTION

THE SYNDROME of hyperosmolar hyperglycaemic nonketotic coma (HHNK) was first recognised by Sament and Schwartz in 1957. Since then more than 200 cases have been reported in the world literature. The condition, however, occurs more frequently than the figure suggests. Over a two-year period at King's County Hospital, for example, 32 patients were admitted with this diagnosis (Arieff and Carroll, 1969). In the Medical Unit III, General Hospital, Kuala Lumpur, two cases were seen over a six-month period. This paper describes these two cases of HHNK diabetic coma and discusses the pathogenesis and management of this condition.

CASE HISTORIES

Case one was a 57 year old Indian man who complained of intense thirst with polyuria and vomiting two weeks prior to admission. He also complained of extreme tiredness and lethargy and was not able to cope with his job as a dishwasher in a hotel. His brother-in-law noticed a change in his behaviour: he was restless and confused and took baths at odd hours as at 2 in the morning.

There was no history of cough, dysuria, fever or abdominal pain. He was not on any medication such as thiazide diuretic, corticosteroids or phenylhydantoins. There was no history of diabetes mellitus, hypertension or epilepsy.

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On examination, the patient was drowsy and confused. He was moderately dehydrated. His blood pressure was 140/100 mm Hg. and pulse rate 100 per min. The temperature was 101°F. and the respiratory rate 20 per min. There was no Kussmaull breathing. The rest of the examination was normal.

His urine was orange for glucose but negative for acetone. The blood glucose was 935 mg%. Blood urea was 75 mg%, sodium 160 mEq/L, potassium 4 mEq/L and chloride 117 mEq/L. Arterial blood gas analysis showed a pH of 7.45 (standard bicarbonate 25 mEq/L), a base excess of +0.5, PO2 70 mm Hg and P CO2 33.5 mm Hg. The electrocardiogram and chest Xrays were normal. Plasma osmolality was not measured but can be calculated from the following formula:—

Plasma osmolality = 1.86 (Serum Na + Serum K) + Blood urea/5.6 + blood glucose/18 mOsm./kg. H_2O.

Substituting the measured values in the above formula, the plasma osmolality of this patient was 370 mOsm/kg. H_2O. The patient, therefore, had features of HHNK diabetic coma namely, glycosuria without acetonuria, hyperglycaemia without ketoacidosis and hyperosmolality.

A small dose of soluble insulan was given intramuscularly and repeated hourly to control the hyperglycaemia. Hydration was achieved with 0.45% NaCl solution and potassium supplement was also given. 90 units of insulin and a total of six litres of fluid were given in the first twenty-four hours by which time the patient was fairly well recovered. Blood glucose was 98 mg%, sodium 140 mEq/L, potassium 4.0 mEq/L, chloride 105 mEq/L and the blood urea 87 mg%. At discharge, his diabetes was well controlled on diet alone, the blood urea was 46 mg% and the serum creatinine 1.0 mg%.

Case two was a 30 year old Indian man who presented with a 10-day history of blurring of vision and was unable to see distant objects clearly. At the same time he experienced intense thirst and was markedly polyuric. He had to empty his bladder almost every half hour. He also felt extremely tired and easily fatigued but observed that he felt refreshed after a bath. He, therefore, took baths fairly frequently and often found it necessary to bathe in the middle of the night. On the morning of admission the patient collapsed while preparing for work and was brought to hospital. There was no history of recent infection or drug ingestion. There was no history of abnormal behaviour or disorientation during this period. There was no past or family history of diabetes mellitus.

On examination, the patient was drowsy but was conscious and rational. He was slightly obese and was moderately dehydrated. The blood pressure was 120/90 mm Hg, pulse rate 102/min. and respiratory rate 18/min. There was no Kussmaull breathing and the temperature was normal. The rest of the examination was normal.

Urine testing for glucose was orange but acetone was absent. The blood sugar was 943 mg%, blood urea 115 mg%, potassium 4.7 mEq/L and chloride 109 mEq/L. Calculated plasma osmolality was 398 mOsm/Kg H2O. The arterial pH was 7.35, standard bicarbonate 20 mEq/L, base excess — 5, pCo2 34 mm Hg, and pO2 92 mm Hg. The haemoglobin was 15.0 gm% and white blood cells 15,000 (neutrophils 70%, lymphocytes 30%). Urine culture on admission was sterile; ECG and chest xrays were normal.

In summary this patient was drowsy and dehydrated, had glycosuria but not acetonuria, had marked hyperglycaemia but without ketoacidaemia. These and the hyperosmolality are features of HHNK.

The diagnosis of HHNK in the second case was only made 8 hours after admission when the biochemical parameters were available. In the meantime, the patient was treated as diabetic ketoacidosis and started on 40 units of soluble insulin intramuscularly. Over the first 24 hours he was given a total of 160 units of insulin and 1800 ml of normal saline. The urine output over the corresponding period was only 200 ml. The next day, the patient went into shock with rapid pulse and unrecordable blood pressure. The blood sugar then was 310 mg% with a blood urea of 120 mg%; serum sodium was 145 mEq/L, potassium 4.4 mEq/L and chloride 110 mEq/L. The patient was resuscitated with rapid I.V. infusion. 4 litres of normal saline were given in the first 6 hours and 10 litres over the 24 hours. The patient's general condition was improved after 7 litres of fluid replacement. His blood pressure came up to 100/80 mm Hg and urine output 800 ml. Blood urea was then at 135 mg%. Serum sodium was 160 mEq/L, potassium 4.0 mEq/L and chloride 137 mEq/L. Normal saline infusion was then changed to hypotonic (0.45% NaCl) solution. During the next two days the patient had a diuresis and blood urea steadily dropped to a normal value. the progress of Case No. 2 is summarised in Fig. 1, 2 and 3.

However, contrary to expectation the patient required high doses of insulin — up to 32 units three times a day to control his diabetes. Urine culture grew Klebsiella organism and after a course of antibiotics, his insulin requirement dropped and on discharge his diabetes was well controlled on diet alone.

Pathophysiology & Pathogenesis of HHNK

Why is there no ketoacidosis in patients with HHNK? Several factors controlling lipolysis contribute to the pathogenesis of HHNK.

Low levels of insulin can inhibit release of free fatty acids from adipose tissue (Arieff *et al.* 1972). Adrenaline, growth hormone, corticosteroids and glucagon on the other hand have adipokinetic properties. Patients who develop HHNK usually have maturity-onset form of diabetes mellitus; a condition usually associated with a high circulating plasma insulin. This is in contrast to juvenile-onset, insulin-dependent diabetes mellitus who are prone to diabetic ketoacidosis. It has been shown by Zierler and Rabinowitz (1964) that at low levels there is a dissociation of the effect of insulin on fat and carbohydrate metabolism. At very low plasma levels insulin has no effect on glucose uptake by cells, yet still can inhibit release of free fatty acid from adipose tissue. Plasma insulin levels measured in HHNK diabetic coma patients prior to theraphy have

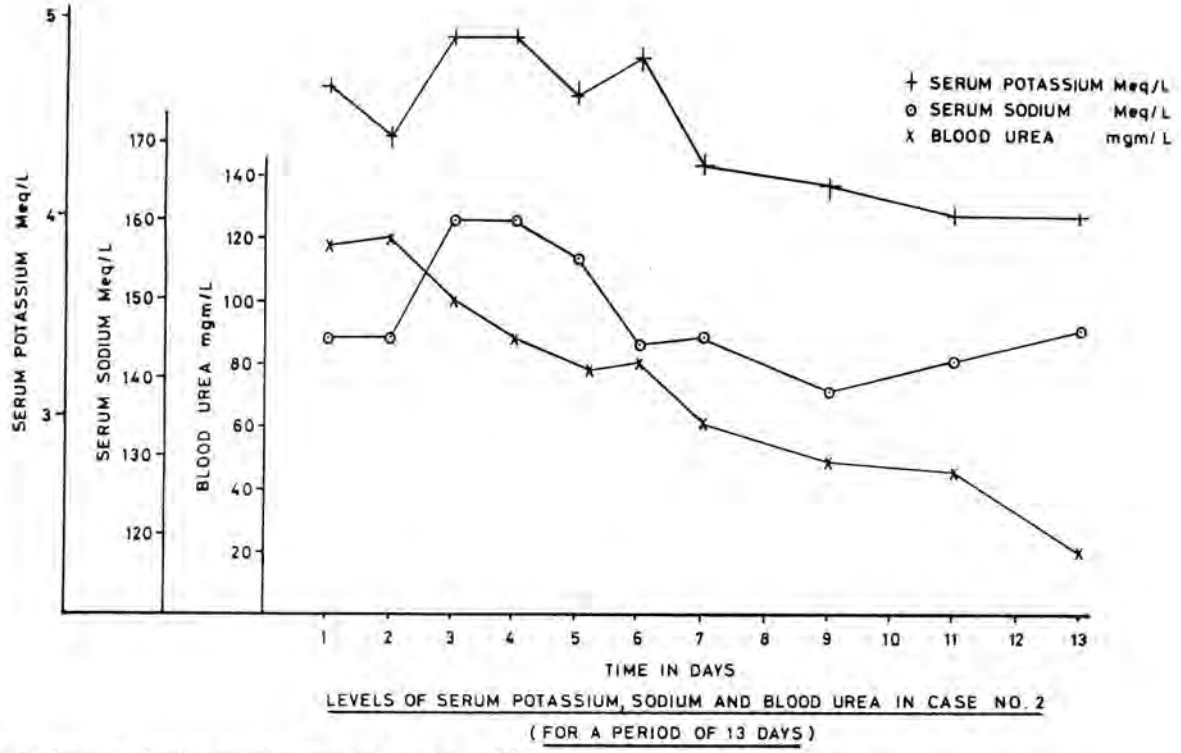

Fig. 1 shows the level of serum potassium, sodium and blood urea over a period of 10 days

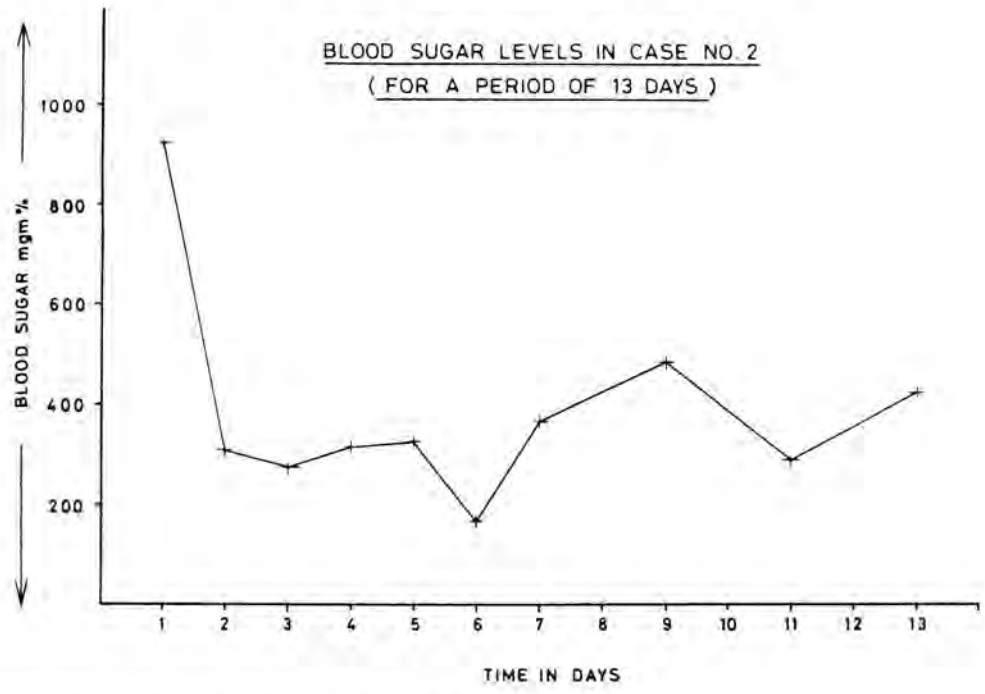

Fig. 2 shows blood sugar levels over the same period of Case No. 2

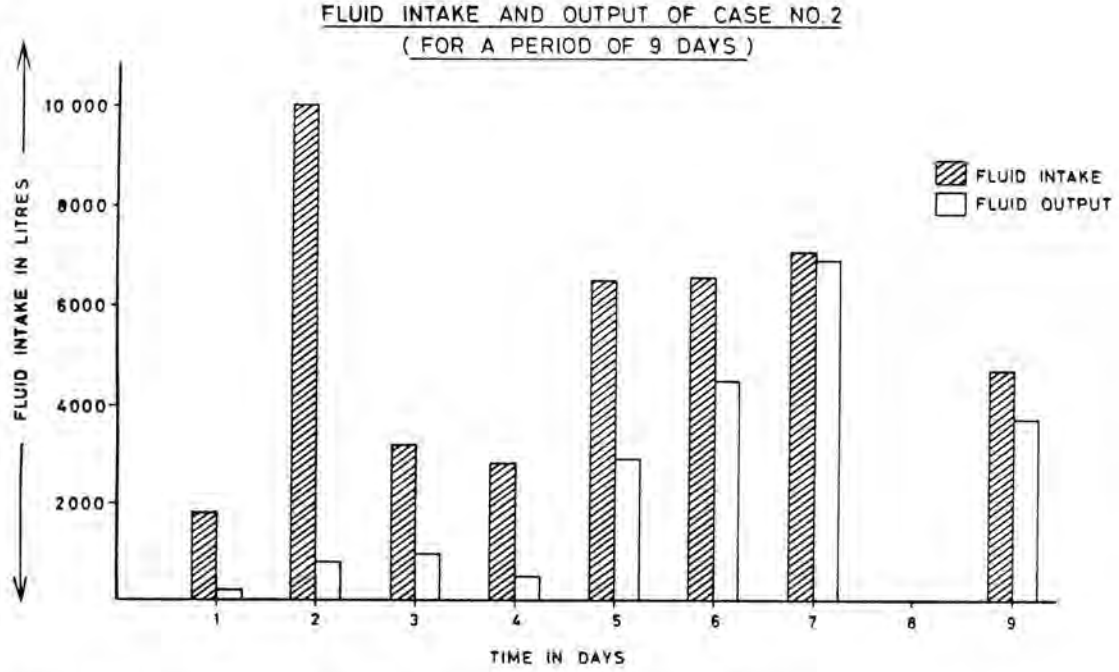

Fig. 3 shows fluids intake and output of the same patient, also for a period of 8 days.

been low. Deficiency of adipokinetic factors such as corticosteroids, adrenaline and growth hormone may contribute to failure of lipolysis, hence the absence of ketosis. Evidence exists that hepatic parenchymal damage causing a block in the conversion of acetyl-CoA to ketoacids may play a role in the absence of ketosis in some cases.

Seltzer *et al.* (1964) infused normal subjects with glucose continuously over several days and showed that they were able to prevent hyperglycaemia by increasing and maintaining high insulin secreting rates. Patients with maturity-onset diabetes mellitus in contrast were unable to maintain a high insulin secretion. In response to a continuous glucose infusion their insulin level peaks by the 2nd day, following which it drops considerably allowing hyperglycaemia to develop. From the above observations and that of Zierler and Rabinowitz (1964) showing the dissociation of the effect of insulin on fat and carbohydrate metabolism, a typical picture of the pathogenesis of HHNK diabetic coma can be drawn. A patient with maturity-onset diabetes mellitus is exposed to some continuous diabetogenic stress such as infection, thiazide diuretics, steroid therapy or a glucose load. Under the constant hyperglycaemia stress, the B-cells eventually fatigue and plasma insulin level drops. Hyperglycaemia worsens but the low level of circulating insulin prevents ketosis. The phase of hyperglycaemia and glycosuria is therefore prolonged allowing the patient time to develop severe dehydration with a marked deficit in water and electrolytes.

DISCUSSION

HHNK diabetic diabetic coma is characterised by stupor, elevation of plasma osmolality, severe hyperglycaemia, and absent ketoacidosis. The average age of patients who develop HHNK diabetic coma is 57 years (Mc Curdy 1970). One of our patients was 30 years. This is uncommon as only 7 cases were reported aged under 40 years (Mc Curdy 1970). In half of the reported series (Mc Curdy, 1970) the onset of symptoms could be traced to some precipitating event as acute gastro-enteritis, acute pancreatitis or ingestion of a drug known to aggravate the diabetic state.

The rapid deterioration of the second case, culminating in a hypovolaemic shock and acute renal failure was most likely precipitated by a rapid lowering of the blood glucose coupled with an inadequate fluid replacement. Before the sodium deficit is corrected the blood glucose is responsible for maintaining a significant fraction of the plasma volume. A rapid correction of hyperglycaemia is thus potentially dangerous as this would rapidly reduce the effective plasma volume, and several authors have reported the development of hypotension early in the course of treatment especially when large doses of insulin had been used.

Patients with HHNK diabetic coma usually have a large fluid deficit averaging up to 8 litres because of the prolonged hyperglycaemia and the persistent osmotic diuresis before they seek medical attention. It is generally agreed that the best therapeutic regimen for most patients is a liberal fluid replacement with hypotonic saline. Insulin therapy should be given cautiously and in low doses. However, if a patient presents in shock, the initial treatment must be with an isotomic saline or a plasma-volume expander regardless of the plasma osmolality.

The mortality of HHNK diabetic coma in reported series is 40-50%. Awareness of this condition with early recognition and appropriate treatment should improve the prognosis.

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