Hyperosmolar non-keto-acidotic diabetic coma

A report of three cases and review of the literature

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Summary

Three further cases of hyperosmotic non-keto-acidotic and non-lactic-acidotic diabetic coma have been described. A favourable outcome in these patients emphasizes the importance of recognizing this condition in its early stages. This may be difficult as there is no ketosis and no hyperventilation—features that one normally associates with diabetic coma. The signs are those of increasing drowsiness, gross dehydration, and occasionally of circulatory collapse, focal seizures and abdominal pain.

Once diagnosed, vigorous treatment must be instituted with large doses of parenteral insulin and intravenous fluids, preferably normal saline initially, followed by mixtures of hypotonic saline and dextrose once the blood sugar has fallen significantly, together with adequate amounts of potassium. In this way it should be possible to reduce the previously high mortality rate.

Introduction

Hyperosmolar non-keto-acidotic diabetic coma was first described by Sament & Schwartz in 1957. Since then some fifty cases have been reported in the world literature but only five cases have been recorded of patients in England (Lucas *et al.*, 1963; Davidson, 1964; Nicholson *et al.*, 1964; Watson, 1966). With an increasing knowledge of the condition two separate types have emerged; those who have lactic acidosis with ketonuria and a plasma bicarbonate level of less than 18 mEq/l (Danowski & Nabarro, 1965) and those who have no acidosis. This condition must also be distinguished from diabetic coma with no initial ketonuria because of renal failure when, in fact, there are ketones in the blood (*Brit. med. J.* Leading article, 1965).

The condition of diabetic coma without keto-acidosis and lactic acidosis is difficult to recognize because of the absence of hyperventilation and the smell of ketones on the breath. It tends to occur in older patients than keto-acidotic dia-

betic coma and usually in previously undiagnosed diabetics. The blood sugar level is very high, usually over 800 mg/100 ml and sometimes over 1500 mg/100 ml. The high rate of glucose excretion in the urine leads to an osmotic diuresis, producing a profound degree of dehydration. This may be so severe as to produce circulatory collapse and intravascular thrombosis. The circulatory collapse may necessitate the administration of plasma or of vasoconstrictor drugs. There may be a marked elevation of the serum sodium concentration and although the serum potassium concentration may be normal initially there may be a profound reduction in the total body potassium, as in keto-acidotic diabetic coma. There is also a significant incidence of focal seizure in this condition (Maccario, Messis & Vastola, 1965; Feagin, 1966; Azerad & Lubetski, 1963; Larcen *et al.*, 1963) and acute pancreatitis has been described (Davidson, 1964; Halmos, 1966).

Three such cases of hyperosmolar non-keto-acidotic and non-lactic-acidotic diabetic coma have been seen in this hospital in the last 3 months (Table 1). These stress the relatively frequent occurrence of these cases, the importance of early diagnosis, and the special problems in treatment, namely, controlling the circulatory collapse, the hyperglycaemia and hyperosmolality and the relative hypokalaemia.

Case 1

A lady of 56 years was admitted in coma with a short history of increasing drowsiness over the previous 3 or 4 days.

On examination she was grossly dehydrated, not ketotic and not hyperventilating. She had an infected varicose ulcer on her left leg. Her BP was 90/70 mmHg. The urine contained >2% sugar but no acetone. Her blood sugar was 730 mg/100 ml, blood urea 200 mg/100 ml, serum sodium 152 mEq/l, serum osmolality 357

TABLE 1

	Case 1	Case 2	Case 3
Age and Sex	56, F	73, F	49, M
History	Increasing drowsiness for 3-4 days	Depression for 4 weeks; increasing drowsiness for 36 hr	Thirst, polyuria for 4 weeks; increasing drowsiness for 12 hr
Examination	Gross dehydration; no ketosis or hyperventilation; slight shock	Gross dehydration; no ketosis or hyperventilation; slight shock	Gross dehydration; no ketosis or hyperventilation; marked shock
Blood sugar (mg/100 ml)	950	860	820
Blood urea (mg/100 ml)	200	118	85
Serum HCO ₃ (mEq/l)	27	34	21
Serum Na (mEq/l)	152	138	123
Serum K (mEq/l)	4.8	2.8	4.5
Serum Cl (mEq/l)	118	100	—
Serum osmolality (mOsm/kg)	357	368	424
Fluid given (litres)	94 (24 hr)	15.5 (36 hr)	15.5
Urine output (litres)	—	3.2 (36 hr)	5.2
Fluid deficit (litres)	—	12.3	10.3
Potassium given (mEq)	121.5	283.5	175.5
Insulin given (units)	270 (18 hr)	150 (12 hr)	242 (12 hr)
Urea returned to normal	7 days	36 hr	36 hr
Sugar returned to normal	18 hr	12 hr	12 hr
Mentally normal	14 days	36 hr	24 hr

mOsm/kg as calculated by the method of Scott (Nicholson *et al.*, 1964). She was given 50 units of soluble insulin intravenously and 2 litres of 1/6th molar lactate in the 1st hour, after which time her blood sugar was 950 mg/100 ml. Then she was given a further 70 units of soluble insulin and 2 litres of normal saline, followed by 5 litres of 4.3% dextrose saline. Her blood sugar returned to normal in 12 hr, after she had been given a total of 270 units of soluble insulin and 121.5 mEq of potassium. Although her electrolytes and blood sugar remained within normal limits she did not recover from her coma for 60 hr. Her blood urea was normal within 7 days but she remained confused and lethargic for 2 weeks. Following this she made a complete recovery and her diabetes was well controlled on 44 units lente insulin. There was no previous or family history of diabetes mellitus.

Case 2

A lady of 73 years was admitted in semi-coma having been increasingly drowsy for the previous 36 hr. She had suffered from lack of concentration and depression for the previous month. She had been treated with methylprednisolone 8 mg daily for 2 years on account of polyarthritis and she had also received a thiazide diuretic for over a year. She had no previous

history of diabetes and no-one in her family had suffered from this complaint.

On examination she was grossly dehydrated, not hyperventilating and not ketotic. Her blood pressure was 110/70 and her urine contained >2% sugar but no acetone. The blood sugar was 860 mg/100 ml, blood urea 118 mg/100 ml, serum sodium 138 mEq/l, potassium 2.8 mEq/l, chloride 100 mEq/l and bicarbonate 34 mEq/l. Her plasma osmolality was 368 mOsm/kg. She was treated with 100 mg hydrocortisone intravenously and 4 litres normal saline followed by 8.5 litres of 4.3% dextrose-saline in the first 36 hr, during which time she passed 3200 ml of urine by catheter. She was given 150 units of soluble insulin in the first 12 hr after which time her blood sugar was within normal limits. Her blood urea returned to normal in 36 hr after which time she was perfectly alert. She was given 283.5 mEq potassium but her serum potassium did not return to within normal limits for 73 hr. Subsequently her diabetes was well controlled on 250 mg chlorpropamide daily by mouth and her polyarthritis was controlled on 8 mg methylprednisolone daily.

Case 3

A man of 49 years was admitted in semi-coma having been increasingly confused and drowsy

for the previous 12 hr. He had complained of thirst and polyuria with constipation and blurred vision for 4 weeks.

On examination he was grossly dehydrated and had a systolic BP of 90 mmHg. His urine showed >2% sugar without acetone and a blood sugar estimation was 820 mg/100 ml, blood urea 85 mg/100 ml, serum sodium 123 mEq/l, potassium 4.5 mEq/l, bicarbonate 21 mEq/l. His haemoglobin was 120% with a PCV of 55%. The plasma osmolality was 424 mOsm/kg. He was treated with 2 litres of normal saline initially followed by a further 2 litres of normal saline and 7 litres of 4.3% dextrose saline in 36 hr and 175.5 mEq potassium. His plasma osmolality and blood urea returned to normal within 36 hr and his blood sugar returned to normal within 12 hr, during which time he had had 242 units soluble insulin. He was mentally alert after 24 hr of treatment. His diabetes was subsequently well controlled on 500 mg chlorpropamide daily.

Discussion

All three of these cases showed a relatively rapid onset of their coma, probably more rapidly than patients in diabetic coma with ketosis; in two of the patients there was no apparent precipitating cause and in the third there were only minor signs of infection in the form of an infective ulcer. It would seem reasonable to treat all cases with parenteral broad-spectrum antibiotics.

A previous history of diabetes mellitus is unusual and has occurred in only five cases in the world literature (di Benedetto, Crocco & Soscia, 1965). None of the present cases was known to be diabetic.

Di Benedetto *et al.* (1965) found that the male-female incidence was approximately 2 : 1 (as in this series) and that the average age incidence was 62 years. They also noted that the premonitory symptoms were invariably increasing drowsiness, polyuria and polydipsia. The present cases illustrate that the onset of coma may be extremely rapid, whereas previously it has been thought that the onset was very prolonged. It is also important to realize that the patients are usually in semi-coma rather than completely comatose despite the high blood sugar. In their review of the world literature di Benedetto *et al.* (1965) found that the average fasting blood sugar was 1145 mg/100 ml serum, the maximum being 2200 and the minimum 460 mg/100 ml. The highest blood sugar in the present series was 950 mg/100 ml and this was presumably due to the relatively early diagnosis of the syndrome. The mortality of the previously reported cases

was approximately 44%. No deaths have occurred in the present cases.

The explanation for the absence of ketosis in these cases is uncertain. There may be a small amount of active circulating insulin in these patients (Matz & Drapkin, 1966), not enough to utilize the excess blood sugar but enough to inhibit free fatty acid release from the fat depots (Zierler & Rabinowitz, 1963). In the view of di Benedetto *et al.* (1965) in diabetic ketosis the liver is the sole source of ketones and a depression in liver glycogen results in the hepatic formation of ketone bodies. When their rate of production exceeds the liver's ability to metabolize them, the ketones accumulate in the blood. Mirsky (Mirsky, Heiman & Brok-Kahn, 1937) has shown that the production of ketone bodies can be inhibited by increasing the level of the blood sugar, which in turn enables the liver to retain adequate stores of glycogen.

The intense dehydration is caused by the glycosuria and the hyperosmolality is caused by the hyperglycaemia. At normal levels the blood sugar does not exert a significant osmotic effect but at great heights it does. Very high blood sugars (over 1000 mg/100 ml) only occur with renal insufficiency according to Matz & Drapkin (1966) and in practically all the recorded cases there has been a significant rise in the blood urea nitrogen concentration. In one of the present cases the blood urea was 200 mg/100 ml. The gross hyperosmolality varied from between 357 and 424 mOsm/kg the upper limit of normal being 300 mOsm/kg.

Hypovolaemic shock is caused by the gross dehydration and the emergency treatment is to infuse plasma-expanding fluids and vasoconstrictor drugs such as metaraminol if necessary, and to correct the dehydration as soon as possible. One of our cases showed marked peripheral circulatory failure, which was controlled by raising the foot of the bed and giving intravenous physiological saline, and the others a mild degree of shock.

It has been said that the insulin requirements are very great (Halmos, Nelson & Lowry, 1966; Sament, 1966). In the present cases this has not been true and the most that one patient required to bring his blood sugar levels to normal was 284 units of soluble insulin. This may be to some extent explained by the early recognition of the condition and relatively low blood sugar levels and partly to the absence of acidosis and hyperosmolality. The rapidity of the response to insulin may be in part due to the absence of acidosis which has recently been shown to produce insulin resistance itself, possibly by its effects on

the structure of the insulin molecule (Butterfield, 1967). Once the patients' diabetes is stabilized they may require little or no insulin and some patients have subsequently shown no diabetic tendency at all (di Benedetto *et al.*, 1965).

There has recently been a great deal of discussion on the management of hyperosmolar coma in diabetes (Watson, 1966; Sament, 1966; Hughes-Davies, 1966; Tovey, 1966; Feagin, 1966). Halmos (1966) treated his cases with 5% dextrose solution intravenously; this has been criticized on the ground that this further raises the blood sugar level and although rehydration may be obtained this may lead to a sodium deficit (Sament, 1966). Since these patients have, by definition, hyperosmolality, solutions isotonic with normal plasma are hypotonic with respect to the patient's body fluids, and therefore tend to correct the hyperosmolality (Rosen & Glick, 1966). The present cases have been treated with between 2 and 4 litres of normal saline given very rapidly over the first 2 hr and then given either 4.3% dextrose-saline if the blood sugar had fallen satisfactorily, or normal saline and 4.3% dextrose-saline. A very large quantity of fluid needs to be given in view of the excessive dehydration, which is well illustrated by the fluid deficits of 12 and 10 litres respectively in the last two cases. It has been possible to reduce the plasma osmolality to within normal limits rapidly by this method. It is important not to be too rigid in treatment.

The problem of the management of the serum potassium has received scant attention in the literature and yet it may well be that hypokalaemia is an important cause of death in these cases. One of the present patients had an initial serum potassium of only 2.8 mEq/l, and this must indicate a very profound reduction in the total body potassium (Abramson & Arky, 1966) bearing in mind the escape of potassium from the cells into the extracellular fluid in uncontrolled diabetes (Hunter, 1966). This patient required the administration of 283.5 mEq potassium before her serum potassium returned to within normal limits.

The prolonged coma in one patient and the prolonged mental confusion in another are difficult to explain, especially as their blood sugar, blood urea and serum electrolyte levels were rapidly reduced to within normal limits. This may be a manifestation of the insult that an arteriosclerotic brain has suffered; alternatively, it may be due to an infarction of the cerebral cortex as in the case recently described by Harding & Turk (1966).

None of the present cases have had focal

seizures, which Maccario *et al.* (1965) described in seven cases and quoted two others in the literature (Azerad *et al.*, 1953; Larcen *et al.*, 1963). Feagin (1966) has described another case. Focal seizures are thought to be caused by the great differential blood/CSF sugar concentration.

The present cases have shown no evidence of pancreatitis which is well documented in diabetic coma with ketosis (Hughes, 1961; Tully & Lowenthal, 1958) and has been described in cases of non-ketotic coma (di Benedetto *et al.*, 1965; Bergos & Hausser, 1964; Halmos, 1966).

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