# HYPEROSMOLAR STATE ASSOCIATED WITH HYPERGLYCAEMIA

## REPORT OF FOUR CASES

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## SUMMARY

Hyperosmolar state associated with extreme hyperglycaemia was diagnosed in four patients within a space of five months. The clinical features, management and outcome of these cases are described. Possible aetiological factors encountered included underlying diabetic state, infection, liver impairment, uraemia, therapeutic hydrocortisone and large glucose intake (orally and by peritoneal dialysis).

Favourable outcome is seen in three patients in whom prompt and energetic treatment of hyperosmolality with 0.45 per cent saline infusion and water orally was instituted. The amount of insulin required to control hyperglycaemia in this condition is much less than in diabetic ketoacidosis.

Hyperosmolar coma, a condition increasingly recognised in clinical practice, is characterised by severe hyperglycaemia, plasma hyperosmolality and absent ketoacidosis. The aetiology is far from clear, although the majority of cases described in the literature were either mild or previously undiagnosed diabetics (Sheldon and Pyke, 1968; Halmos, Nelson and Lowry, 1966; Schwartz and Aptelbaum, 1965) and precipitating factors such as infection, stress or large ingestion of carbohydrates are often present (Schwartz and Aptelbaum, 1965; DiBenedetto, Crocco and Soscia, 1965). As the prognosis of this condition is determined largely by the rapid institution of appropriate treatment, the following report of cases aims to draw attention to its occurrence in local clinical practice in order that early diagnosis and treatment might avert the known potentially lethal outcome.

## CASE REPORTS

The four cases described were diagnosed within a period of five months in 1969. All of them occurred in the background of severe systemic illness.

### Case 1

A 48 year-old Chinese woman was admitted to Hospital with a history of fever, headache, polydipsia and polyuria for one week and mental confusion on the day of admission. There was no past history of diabetes mellitus. On examination, she was febrile (102.6° F), pale, tremulous and disorientated. Pulse was 130/min., and blood pressure, 130/70 mm. Hg. There were no other physical signs of note. Urine test with Benedict's solution was orange. No acetone was however present in the urine. Blood sugar was 1088 mg./100 ml.; serum alkali reserve, 28 volumes per cent; and blood urea, 86 mg./100 ml. Microscopic examination of urine revealed 80-100 pus cells per high-power field. She was treated with soluble insulin, 4.2% sodium bicarbonate and normal saline. However, she deteriorated rapidly and died 7 hours after admission. Her blood sugar just before death was 760 mg./100 ml.

### Comments

The lack of response to the treatment given, together with the very high blood sugar and absent ketonuria strongly suggest a hyperosmolar state which unfortunately could not be confirmed by measuring plasma osmolality. Lacticacidaemia is another possibility but the lack of response to sodium bicarbonate is unusual. This patient was the first of the present series of cases with hyperosmolar state.

### Case 2

A fifty-year-old man was admitted to hospital and diagnosed clinically as a case of Leptospirosis. This was confirmed by a positive S.E.L. (Sensitised Erythrocyte Lysis) test with a titre of 1/400 which subsequently rose to 1/6,400. He was jaundiced and serum bilirubin was 8 mg./100 mls.; S.G.P.T. was 255 King's units (normal 70-130 King's units); alkaline phosphatase, 12.8 K-A units; serum albumin, 2.8 gm./100 ml. and serum globulin, 3.4 gm./100 ml. A routine Benedict's test for sugar in the urine was negative. His urine output rapidly dropped and he became anuric and oedematous on the 4th day in hospital. Blood urea correspondingly increased and was 204 mg./100 ml. with the onset of anuria. At this time, his serum sodium was 122 mEq./L; potassium, 4.5 mEq./L and chloride, 92 mEq./L.

Peritoneal dialysis was commenced at this stage. Altogether, over 48 hours, he had 51 exchanges, of which 18 were with 1.5% glucose dialysate, and 33 with 4.25% dialysate.

A total of 2,145 ml. of excess fluid was withdrawn evenly over the period of dialysis. His post-dialysate blood urea was 110 mg./100 ml.; serum sodium, 134 mEq./L; serum potassium, 4.7 mEq./L and serum chloride, 98 mEq./L. However, his general condition did not improve with dialysis and instead he became more restless and confused with generalised body twitching. Urine output was good during and after dialysis, rising from 950 ml. on the second day of dialysis to 3,300 ml. on second post-dialysis day. Blood pressure remained steady at about 130/80 throughout. He was not clinically dehydrated or dyspnoeic, and took about 2,000 gm. of glucose orally in the first two post-dialysis days.

On the third post-dialysis day, as his condition continued to deteriorate, a lumbar puncture was done, which yielded cerebrospinal fluid with the following values: urea, 157 mg./100 ml. and glucose, 520 mg./100 ml. Blood sugar was found to be 1420 mg./100 ml. Urine was orange with Benedict's test, but contained no acetone. Serum sodium was 151 mEq./L, serum potassium, 5.4 mEq./L and serum chloride, 120 mEq./L. Plasma osmolality was 363 mOsm./kg. All dietary carbohydrate was withdrawn, half-strength normal saline was rapidly infused and soluble insulin exhibited. There was satisfactory response to treatment. When patient regained normal mental function on the 4th day of treatment, a total of 18 litres of fluids had been administered (7.5 litres half-strength normal saline intravenously and 11.5 litres water orally). Random blood sugar at this stage was 278 mg./100 ml. His diabetic state continued to improve and insulin was finally withdrawn to observe the change in diabetic status. Meanwhile with crystalline penicillin injections, infection came under control, liver function gradually improved and jaundice cleared up while renal function returned to normal.

One and a half months later, a normal glucose tolerance test was obtained (zero hour, 110 mg./100 ml.; one hour, 145 mg./100 ml.; 2 hour, 127 mg./100 ml.). Blood urea then was 16 mg./100 ml. and S.G.P.T. 125 King's units. Cortisone-glucose-tolerance test carried out ten days later, however, was abnormal (zero hour, 105 mg./100 ml.; one hour, 185 mg./100 ml.; two hour, 200 mg./100 ml.). The patient has no past or family history of diabetes mellitus.

**Comments**

Diagnosis here is confirmed by measurement of plasma osmolality. The combination of infection, uraemia, liver impairment, glucose loading orally and during dialysis and underlying subclinical diabetes must have been responsible for the hyperglycaemia. As the first four factors are commonly present in severe Leptospirosis, the complication of hyperosmolality must be constantly borne in mind. It is surprising, however, that no report of such a complication has been encountered in the literature.

**Case 3**

A 54-year-old man was admitted to hospital with a history of fever with rigors and colicky abdominal pain for ten days. He gave no past or family history of hypertension or diabetes, although on admission, his urine was green with Benedict's solution. On examination he was jaundiced and febrile (100.4° F). Liver was enlarged (3 finger-breadths) and tender. There was no neurological deficit. His blood pressure was 110/70. Soon after admission, his blood pressure dropped to 70/50 and he developed ileus. He was treated as a case of cholangitis with septicaemic shock. A laporotomy was carried out for a suspected pelvic abscess. No abscess, however, was found; the liver and spleen were found to be enlarged, and straw-coloured ascitic fluid was present. A liver biopsy was done which showed the histology of cholangitis.

During laparotomy and post-operatively, intravenous hydrocortisone was given together with Ampicillin. His blood pressure improved and was maintained at 110/70. However, patient became irritable and on the eight post-operative day was delirious and disorientated. Serum bilirubin was 1.8 mg./100 ml. and S.G.P.T. 237 King's units (normal: 70-130). A total of 4000 mg. of hydrocortisone had been given to the patient. Lumbar puncture yielded a C.S.F. whose glucose concentration was 410 mg./100 ml. Blood sugar was 780 mg./100 ml. Urine was orange with Benedict's solution but contained no acetone. Alkali reserve was 65 volumes per cent. Serum Na was 167 mEq./L. He was promptly treated with half-strength normal saline intravenously and soluble insulin. When his mental symptoms abated 14 hours later he had received 7 litres intravenous half-strength normal saline. Meanwhile his blood sugar had come down to 261 mg./100 ml. after only 40 units of insulin in 2 divided doses. Serum Na at this stage was 143 mEq./L; serum K, 3 mEq./L; and serum Cl, 118 mEq./L. Thereafter, the daily requirement of

insulin was not more than 30 units per day, and 2 weeks later, his diabetes could be controlled with tolbutamide 500 mg. b.d.

Meanwhile the infection came under control and the patient was discharged after a total stay in hospital of one and a half months.

**Comments**

The patient was presumably a mild diabetic to begin with and in the course of his current illness, developed hyperosmolar state. The possible precipitating factors were infection, liver disease and large doses of hydrocortisone intravenously. The clinical picture, the absence of ketosis and acidosis, the high blood sugar level, the high serum sodium level and the satisfactory response to treatment with large volumes of hypotonic solution and relatively small doses of insulin—all point to the unequivocal presence of the hyperosmolar state. Having come out of the hyperosmolar state, he required only tolbutamide 500 mg. b.d. for control of his diabetes.

**Case 4**

A 40-year-old Chinese housewife was admitted to hospital with a history of giddiness, vomiting and blurred vision for one week and purulent sputum, severe polydipsia and polyurina for 2 days. She had no past or family history of diabetes or hypertension, although she admitted that for 4 months she had noticed increased thirst.

On examination, she was febrile (99° F) and had coarse crepitations in both lung bases. Her blood pressure was 150/110. She was not dyspnoeic or dehydrated. Other than absent ankle and knee jerks on both sides, no neurological signs were found. Fundal examination revealed silver-wiring only.

Urine was orange on testing with Benedict's solution. No acetone, however, was found in the urine. Blood sugar was 920 mg./100 ml. Blood alkali reserve was 62 volumes per cent; blood urea, 62 mg./100 ml. Urine culture grew streptococcus faecalis while sputum grew Staphylococcus aureus. E.C.G. showed non-specific S.T. flattening in $V_5$, $V_6$.

She was treated promptly with half-strength normal saline, soluble insulin and antibiotics (tetracycline, followed by penicillin and streptymycin). In the first 15 hours, she had 5 litres half-strength normal saline intravenously and 4 litres water by mouth, and 102 units soluble insulin. The blood sugar was brought down to 327 mg./100 ml., and her general condition markedly improved. Giddiness and vomiting stopped but she remained polydipsic and polyuric. After 2 weeks in hospital, she was discharged on a maintenance dose of I.Z.S. (lente) 60 units per day. Meanwhile infection had been controlled and her B.P. on discharge was 110/80.

**Comments**

This patient was most probably diabetic before the onset of the hyperosmolar state. Chest and urine infections were likely precipitating factors. The very high blood sugar level and the absence of acidosis and ketosis strongly suggest a hyperosmolar state. The latter was confirmed by the response to treatment with hypotonic solution and relatively small doses of soluble insulin.

## DISCUSSION

The frequency of this condition locally is well illustrated. It is perhaps a little surprising that such a high incidence (four cases in five months) had not been previously met with, at least, in this Medical Unit. Lack of awareness had accounted for the delay in diagnosis in some of the cases reported. As all the cases cited occurred in the background of some systemic illness, hyperosmolar state might be regarded as a complication of certain diseases in certain people.

The possible precipitating factors in the cases have been mentioned. Infection is known to impair glucose tolerance and must have contributed to the severe hyperglycaemia in all the cases. As uptake of glucose by the liver is one of the factors in glucose homeostasis (Boukaert and De Duve, 1947; Pyke, 1968), liver impairment as occurred in two cases, might have aggravated hyperglycaemia. Case 2 is unique in that he was uraemic, was dialysed with hyperosmotic fluid (4.25 per cent glucose dialysate) and ingested large amounts of glucose just prior to diagnosis. Uraemia is known to be associated with poor glucose tolerance (Hutchings, Hegstrom and Bernstein, 1966), while the use of hypertonic dialysate imposed a heavy load on glucose homeostasis. Using the data of Boyer, Gill and Epstein (1967), the total glucose absorbed over the period of dialysis (48 hours) would be about 1.6 kg. The latter, together with the large oral glucose intake (2 kg.) in the immediate post-dialysis period, must have significantly contributed to the severe hyperglycaemia.

The contribution of large therapeutic doses of intravenous hydrocortisone to hyperglycaemia is probably important in Case 3. In this case, as in Case 2, the several possible hyperglycaemic influences must have potentiated one another to produce the extreme hyperglycaemia.

According to Sheldon and Pyke (1968), hyperosmolar coma is seen more common in new diabetics than in established cases, as over three-quarters of cases reviewed have not been previously diagnosed. This is confirmed by the cases described here. Cases 1 and 2 certainly had no history of diabetes while Cases 3 and 4 were mildly diabetic. Cases 2 became free of symptoms and signs of diabetes after the hyperosmolar episode but his cortisone-glucose tolerance test was abnormal. The true diabetic status of those patients who finally become free of clinical signs of diabetes has not been investigated for the cases reported in the literature (Halmos, Nelson and Lowry, 1966; Maccario, Messis and Vastola, 1965) and it is not clear whether the hyperosmolar state can occur as temporary events in otherwise normal persons.

The mainstay in treatment is to rapidly infuse hypotonic solutions to combat hyperosmolality. This should be supplemented by water orally, if tolerated. The most commonly used hypotonic solution is half-strength normal saline, and as in the cases described, large volumes are normally required especially in the first few hours. Insulin therapy is important, but the absence of acidosis means that response is more sensitive and prompt than in diabetic ketoacidosis. Moreover, there is significant endogenous insulin production in hyperosmolar state (Sheldon and Pyke, 1968). The amount of insulin required is relatively small for the degree of hyperglycaemia present.

The absence of ketosis has been a subject of much research and controversy. Lexow (1959) believes that it is attributable to hepatic dysfunction secondary to shock. Although Cases 2 and 3 were not in shock when hyperosmolality came on, they certainly had significant hepatic impairment.

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