in the elucidation of primary morbidity. The differentiation between changes due to nephrosclerosis, chronic nephritis, and chronic pyelonephritis can be difficult, and the final diagnosis has been reached on correlations between histological, radiological, and bacteriological findings, together with the clinical picture. Focal nephritis has been associated with hypertension (Kincaid-Smith, 1966). The exact pathophysiological significance of this is not clear, though a familial type with dominant inheritance associated with severe hypertension has been described. Finally, this study emphasizes the need to investigate young hypertensive patients, especially those who are under the age of 35 or who have fundal grades III and IV hypertension, as a large proportion of these will be found to have an underlying cause.

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Reversible Cerebral Oedema Complicating Diabetic Ketoacidosis

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Summary: A young man with diabetic ketoacidosis developed the clinical features of cerebral oedema. This resolved without specific treatment. The mortality from ketoacidosis might be reduced if the syndrome was suspected and treated earlier.

Introduction

The mortality from diabetic ketoacidosis varies between 8 and 16%, depending on the age of the population studied (Greenway and Read, 1958; Fitzgerald *et al.*, 1961; Young and Bradley, 1967). At necropsy many of these patients show the pathological characteristics of cerebral oedema. This syndrome, however, has seldom been considered or diagnosed by the clinician, and the pertinent literature deals mainly with its pathogenesis and irreversible course. We wish to draw attention to a patient with this condition who recovered spontaneously. Retrospective consideration of the clinical progress of other patients with diabetic ketoacidosis leads us to believe that this syndrome may not be very uncommon.

Case Report

An 18-year-old negro was brought to Billings Hospital emergency room moderately confused and lethargic. His wife stated that until two weeks previously he had been in excellent health. He then developed weakness, malaise, weight loss, shortness of breath, polyuria, and polydipsia. He complained of abdominal pain, nausea, and recurrent vomiting. There was no history of trauma or infection. His maternal grandmother had diabetes mellitus requiring insulin.

On physical examination he was lethargic, thin, and profoundly weak, with pronounced Kussmaul respiration. His pulse was 136/minute, blood pressure 115/70, respiration 36/minute, and rectal temperature 37°C. He was dehydrated, and acetone was noted in his breath.

Initial laboratory data included a blood sugar of 765 mg. and blood urea nitrogen of 22 mg./100 ml.; the serum sodium was 130 mEq, potassium 5.2 mEq, chloride 92 mEq, and bicarbonate less than 10 mEq/l. The calculated serum osmolality was 328 mOsm/l. (Dillon *et al.*, 1936). Serum acetone was 3+ at 1:2 dilution with Acetest tablets. Arterial blood gases were CO₂ 12 mm.

and O₂ 118 mm. Hg; the pH was 7.25. The packed cell volume was 51% and the white blood count 21,500 cells/cu.mm., with 95% polymorphonuclear leucocytes.

Intravenous therapy was initiated with 1 litre of 0.45% saline to which 44 mEq of sodium as bicarbonate was added; concomitantly, 100 units of regular insulin was injected subcutaneously. Over the first four hours he received 3 litres of 0.45% saline and 88 mEq of sodium bicarbonate. The blood sugar fell to 376 mg./100 ml., serum acetone decreased to 1+ without dilution, and the serum bicarbonate rose to 10 mEq/l. Serum sodium, potassium, and chloride levels approached normal values. At this time he was alert, but complained of nausea and vomited. During the next four hours 50 units of regular insulin, 2.5 litres of 5% dextrose in 0.33% saline, 88 mEq of sodium bicarbonate, and 80 mEq of potassium chloride were given. The blood sugar fell to 240 mg./100 ml., serum bicarbonate increased to 21 mEq/l., and serum acetone was negative. His mental status improved noticeably and headache, nausea, and vomiting abated. He remained afebrile and had a satisfactory urinary output.

About 10 hours after admission his mental status suddenly worsened despite near normal serum electrolyte (sodium 133 mEq, potassium 3.7 mEq, chloride 101 mEq, bicarbonate 21 mEq/l.) and blood glucose values (200 mg./100 ml.). The serum osmolality was 295 mOsm/l. He complained of headache and became lethargic, confused, and difficult to arouse. Moderate neck stiffness was elicited, but neither papilloedema nor localizing neurological signs were observed. Lumbar puncture revealed an opening pressure of 420 mm. and a closing pressure of 410 mm.; there were no cells, and all cultures were subsequently negative. The cerebrospinal fluid protein was 25 mg. and glucose 270 mg./100 ml. The simultaneous blood sugar value was 176 mg./100 ml. A diagnosis of cerebral oedema was made, and though treatment with mannitol and steroids was considered we decided to observe his course for a short time before their administration. Gradually over the next four hours the patient improved: he became less irritable, was more alert, and began to converse rationally and spontaneously. Thereafter he showed steady improvement, and some eight hours after the lumbar puncture his mental status returned to normal. The remainder of his stay in hospital was uneventful, and after two weeks he was discharged on 24 units of insulin injection and 24 units of protamine zinc insulin injection daily. At later outpatient visits neurological examination was negative and his mental status was normal.

Discussion

This report illustrates the occurrence of cerebral oedema complicating the management of moderately severe diabetic ketoacidosis. The clinical picture of mental deterioration

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showed no evidence of circulatory collapse or infection and serum electrolytes and blood sugar values were only minimally deranged. The case is unusual because of the recognition and documentation of the syndrome and its subsequent spontaneous reversibility.

Cerebral oedema complicating diabetic coma has only recently received significant attention (Fitzgerald *et al.*, 1961; Young and Bradley, 1967; Hayes and Woods, 1968). These authors reported six patients with the characteristic clinical picture; all were young (aged 9 to 28), with moderately severe ketoacidosis (blood sugar 500 to 800 mg./100 ml.), and after an initial short period of improvement (4 to 16 hours) mental deterioration and death occurred secondary to histologically proved cerebral oedema. It is of particular interest that the presence of cerebral oedema at necropsy had been noted in several earlier publications dealing with ketotic diabetics who died for "unexplained reasons" (Dillon *et al.*, 1936; Di Benedetto *et al.*, 1965; Hayes and Woods, 1968). Nevertheless, the clinical syndrome was neither recognized nor correlated with the pathological findings. Though Young and Bradley (1967) suggested that the occurrence of cerebral oedema in hyperglycaemic hyperosmolar coma was unlikely, Maccario *et al.* (1965) reported the development of this syndrome in such a patient who survived. In this context cerebral oedema has also been documented histologically in patients dying with hyperosmolar non-ketotic coma (Larcon *et al.*, 1963; Bergoz and Hausser, 1964) and recognized in hypoglycaemic coma (Marks and Rose, 1965).

The pathogenesis of cerebral oedema in patients with diabetic ketoacidosis is still uncertain. Dehydration, haemoconcentration, acidosis, and decreased cerebral blood flow lead to cerebral anoxia and suppression of aerobic metabolism (Meyer *et al.*, 1965). Brain cells may become abnormally permeable to sodium ions, and water would follow owing to osmotic pressure gradients (Young and Bradley, 1967; Hayes and Woods, 1968); the result would be intracellular overhydration. Recent studies have suggested that increased activity of the polyol pathway in response to hyperglycaemia results in accumulation of osmotically active fructose and sorbitol in the brain (Clements *et al.*, 1968). The time of occurrence of this complication also suggests many similarities to the disequilibrium syndrome, which may develop during dialysis. Though we have carefully assessed the rate at which our patient's osmolality, acidosis, and hyperglycaemia were corrected, as well as the quantities of

sodium, bicarbonate, and water administered, we can find no features to distinguish his therapy from that of our patients who did not develop this syndrome.

Therapy usually recommended for cerebral oedema is urea or mannitol together with glucocorticoids (Matson, 1965). This regimen, however, has been tried with little success in a few instances of cerebral oedema complicating diabetic ketoacidosis (Young and Bradley, 1967). Because of the high mortality from the condition we feel that this mode of therapy needs further evaluation. If there was no improvement in a patient with cerebral oedema after a short period of observation, or if the patient was comatose at the time of diagnosis, we would recommend the use of these drugs. In our patient improvement was rapid and progressive after the diagnosis was made; for this reason, as well as the fact that anti-oedema agents have not always proved beneficial, therapy was withheld.

If this syndrome is to be recognized careful and frequent monitoring of the neurological status of patients treated for diabetic ketoacidosis is necessary. Posner *et al.* (1965) have drawn attention to the interrelationships of blood and cerebrospinal fluid acid-base balance in diabetic ketoacidosis uncomplicated by this syndrome. Simultaneous measurements of blood and cerebrospinal fluid glucose, osmolality, pH, and electrolytes will undoubtedly facilitate our understanding and treatment of cerebral oedema.

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Preliminary Communications

Free Amino-acid Concentrations in Fetal Fluids

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Summary: The pattern of free amino-acid concentrations in maternal venous plasma, fetal umbilical arterial plasma, fetal urine, and amniotic fluid at 15 to 20 weeks' gestation has been determined. Free amino-acid concentrations were greater in fetal plasma than in maternal plasma, amniotic fluid, or fetal urine.

The ratios of amino-acid concentrations in fetal umbilical arterial plasma and urine indicate that the fetal kidney can effectively conserve amino-acids, possibly reaching an adult level of competence in this respect.

There was little correlation between amino-acid concentrations in the fluids analysed with the exception of that between amniotic fluid and fetal urine.

INTRODUCTION

Patterns of urinary free amino-acid excretion have been established for adult man, the newborn infant, and a number of different animal species (Evered, 1956, 1967; O'Brien and Butterfield, 1963). Such patterns are characteristic but can be altered by pathological states. Thus urinary patterns may be disturbed by renal tubular defect or when plasma concentrations of individual or groups of amino-acids exceed the renal tubular threshold (Dent, 1954).

The purpose of this paper is to describe the pattern of plasma and urinary amino-acid concentrations in the fetus during early pregnancy, to relate these to maternal amino-acid concentrations, and to assess their influence on the composition of amniotic fluid.

MATERIALS AND METHODS

Samples were obtained at hysterotomy pregnancy terminations between 15 and 20 weeks' gestation. The eight mothers