DIABETES MELLITUS WITH ADDISON'S DISEASE

A CASE REPORT

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In the last 20 years, the role of the pituitary and suprarenal glands in the aetiology of diabetes mellitus has become increasingly apparent. Nevertheless, there are many points still not fully understood, among which should be mentioned the part played by the glands of internal secretion in the production of some of the complications of the disease such as ketosis and vascular degeneration.

Since Arnett[1] (1927) reported the first well-documented case of diabetes mellitus and Addison's disease occurring together in the same patient, 43 further cases have been recorded in the English literature.[2, 3] In 29 the diabetes preceded the onset of Addison's disease, in 4 the 2 diseases seemed to appear simultaneously, and in the remaining 10 cases the Addison's disease occurred first. The case presented here is, as far as is known, the first of its kind to be described in South Africa.

CASE REPORT

The patient is a 35-year-old White male, resident in Swaziland and an electrician by trade. He was first seen in November 1954. He is married and has one child. A brother is diabetic. There was no history of exposure to tuberculosis. The patient had suffered from diabetes mellitus since the age of 3 and for many years was very well controlled on 12-14 units soluble insulin before breakfast and 16-20 units soluble insulin at night. Insulin reactions were very rare. Diet was not strict since the patient was under-weight, but he avoided sugar and starches where possible. He had been in exceptionally good health until the middle of September 1954, when he began to complain of excessive tiredness, fatigue, lassitude and poor appetite. His weight had dropped from 160 to 145 lb. in 1½ months. He had returned from a fishing trip a month before the onset of symptoms and his wife had often remarked on the persistence of his sun-tan. The patient had also recently reduced his insulin dosage a little because he tended to 'see black for a second or two' on exertion.

Examination showed the patient to be a slender individual with well-marked brown pigmentation of exposed areas of the body and also the nipples, perineum, gums and palate. The blood pressure was 105/70 mm. Hg. The knee jerks were reduced and the ankle jerks were absent. Axillary and pubic hair were not decreased in amount and the genitalia were healthy. The fundi showed no evidence of degeneration characteristics of the late manifestations of diabetes mellitus. The rest of the clinical examination showed nothing of significance.

Investigations

A blood count and E.S.R. were normal. The fasting blood sugar was 250 mg.% and a standard glucose-tolerance curve was diabetic with a 3-hour-value of 537 mg.%. Thorn's test, using 25 mg. ACTH, showed an initial eosinophil count of 140 per c.mm.; 4 hours later it was 160 per c.mm. Radiography of the chest, abdomen, pituitary fossa and gastro-intestinal tract showed nothing abnormal. The volume of urine collected 5 hours after a water load of 1,500 ml. was 340 ml. Urinary 17-ketosteroid excretion was 5 mg. in 24 hours and F.S.H. excretion was 6-12 mouse units in 24 hours. Thymol turbidity, 2 units; thymol flocculation, negative. The pathologist's report on the skin biopsy read: 'Sections show excessive melanin pigmentation in the basal layers of the cells of the epidermis. However, the picture is not necessarily pathological. No evidence of haemosiderin pigmentation was demonstrated.'

The diagnosis was made of Addison's disease superimposed on a long-standing diabetes mellitus on the basis of the clinical history and examination, which was supported by the above laboratory findings.

Treatment was commenced with intramuscular injections of 5 mg. desoxycorticosterone acetate (DCA) daily and he was maintained on 15-20 units of insulin a day. No special diet was prescribed. He experienced an initial clinical improvement on this regime but after 4 weeks insulin reactions became frequent. Because of this, cortisone acetate 25 mg. daily was added. Later a 2,100-calorie diet was prescribed with the carbohydrate-fat ratio of 2 : 1 and DCA implants were substituted for the intramuscular injections in August 1955.

During 1955 he remained fairly well but insulin reactions were frequent. He was taking between 18-40 units of insulin daily. The blood pressure varied between 140-155/70-90 mm. Hg. and he was maintaining his weight after an initial gain of 8 pounds. In August 1955 the serum electrolytes were normal.

In February 1956 400 mg. DCA was implanted because of

loss of 10 pounds in weight and a blood pressure of 100/70 mm. Hg. He was taking only 10 units of insulin a day but was still having hypoglycaemic attacks. A further DCA implant was inserted in June 1956.

He was admitted to a Johannesburg nursing home in July 1957 in early diabetic ketosis. After control, cortisone was discontinued and he was discharged on 40 units of insulin daily; 400 mg. of DCA was implanted and this was repeated in October 1957, at which time his insulin requirements had increased to 66 units daily.

On 1 November 1957 at 7 p.m. the patient was admitted to the Johannesburg General Hospital having been in deep coma for 5 hours. The blood pressure was 200/110 mm. Hg and the pulse rate 84 per minute. Physical examination was negative. He was not dehydrated and the breathing, although stertorous, was not Kussmaul in character. Urinanalysis showed no sugar, acetone or albumin. The blood sugar was 45 mg.%. He was given 150 ml. of 50% glucose intravenously with improvement in the level of consciousness. An infusion of 10% glucose in water was begun and urine was tested 2-hourly. Cortisone and salt were withheld at this stage because of the high blood pressure.

By 4 a.m. the following morning the patient had again lapsed into deep coma. He was cold and clammy and the blood pressure was 140/70 mm. Hg. The breathing was now acidotic and he was markedly polyuric. There was 4+ sugar and 2+ acetone in the urine and the blood sugar was 412 mg.%. Serum potassium was 3·5 mEq/litre and the serum CO_2 content was 16 mEq/litre. He was thus in typical diabetic coma. Thirty units of soluble insulin were given immediately by the intravenous route, subsequent doses being administered subcutaneously every 3 hours according to the scheme of 5 units per plus of glycosuria. Two litres of physiological saline and 3 litres of glucose saline were infused over the next 8 hours. Hydrocortisone 100 mg. was added to the first litre, 75 mg. subsequently into each of the following 4 vacolitres. Thereafter he was given 25 mg. hydrocortisone intramuscularly every 6 hours for 24 hours, and was then maintained on 25 mg. cortisone acetate daily by mouth. After 24 hours the serum-potassium level had dropped to 2·5 mEq/litre and 6 g. of intravenous potassium chloride was given slowly over a period of 12 hours. The patient responded very well and after 2 days was fully recovered. Subsequent therapy included removal of the DCA pellets and an attempt to control the diabetes with soluble insulin, cortisone and salt. The diabetes remained very unstable but the patient had to be discharged from hospital 3 weeks after admission. On discharge he was taking 25 mg. of cortisone acetate and 60 units of insulin daily.

He lives at a distance and by correspondence says he is well except for frequent attacks of mild hypoglycaemia. He has consequently reduced the insulin to 28-30 units a day but has not changed the dose of cortisone.

DISCUSSION

This is an undoubted case of Addison's disease developing in a patient with diabetes mellitus. The diabetes commenced at the age of 3 years and it was only 32 years later that symptoms of adrenal insufficiency became manifest. Simpson[2] describes a similar case and comments that the long interval between the appearance of the two diseases seems to preclude a common aetiology.

As in other cases in the literature where the diabetes preceded the Addison's disease, important features heralding the onset of the Addison's disease were the sudden instability of the diabetes, the increased tendency to hypoglycaemic reactions, and the progressive reduction in insulin requirements.

The exact mechanism of action of insulin is unknown but it seems likely that its effect on carbohydrate metabolism is mediated partly through the facilitation of the hexokinase reaction in the phosphorylation of glucose to glucose-6-phosphate and partly through enhancing cellular permeability to glucose. The anterior pituitary seems to antagonize these actions and the adrenal cortex appears to augment this inhibition.[3, 4] In diabetes there is an increase in the breakdown of protein and liver glycogen to glucose, glycogen formation from glucose is greatly reduced in liver and muscle, and this is shown clinically by the poor glucose tolerance, the hyperglycaemia and the glycosuria.

In Addison's disease the hypoglycaemia which occurs is probably not due to defective alimentary absorption of carbohydrates. DCA restores intestinal absorption to normal levels, but exerts a negligible beneficial effect on the hypoglycaemic tendency. The maintenance of adequate liver-glycogen stores and the prevention of fasting hypoglycaemia seems to be a specific function of the glucocorticoids. Clinically the effect of adrenal cortical deficiency on carbohydrate metabolism is shown by abnormally low fasting blood-sugar levels, marked insulin sensitivity, and hypoglycaemic reactions occurring often at higher blood-sugar levels than in a patient with normal suprarenal function. The oral glucose-tolerance curve is flat and the intravenous glucose-tolerance test shows a normal rise followed by a rapid fall to hypoglycaemic levels.

It has been demonstrated that diabetes mellitus, produced in animals by pancreatectomy, can be ameliorated by hypophysectomy or bilateral adrenalectomy.[5, 10] The human equivalents of the Houssay phenomenon are rare indeed. Forty-three cases of Addison's disease and diabetes occurring in the same patient have been recorded and there are even fewer reported cases of hypopituitarism and diabetes occurring simultaneously.

When Addison's disease complicates the diabetic state, gluconeogenesis is diminished; more glucose is utilized by the tissues, blood sugar levels are lowered and glycosuria is reduced. Further, there is progressive improvement in carbohydrate tolerance but the blood-sugar levels are markedly unstable as if the mechanism for blood sugar regulation is in some way additionally disturbed because, though tending on the whole to be lower, the levels are not kept within physiological limits of variation. This is in keeping with the experimental evidence that the adrenal cortex *via* the glucocorticoids plays an important part in such regulation. Moreover, insulin requirements diminish, insulin sensitivity is great and insulin reactions are frequent.

Patients suffering from both diabetes and Addison's disease rarely develop ketosis. Protein catabolism probably plays a greater roll in the genesis of ketone bodies than is generally thought. When insulin is withheld from depancreatized animals, somatotrophic hormone assumes a catabolic function and increased mobilization of amino acids from protein results. It is possible that the ketosis which occurs under these circumstances is due, to a large extent, to the excessive deamination of the pool of amino acids. A few amino acids, like leucine, are directly ketogenic whilst others, like glutamic acid, normally give rise to alpha-ketoacids. Due to the block in carbohydrate metabolism caused by insulin deficiency these alpha-ketoacids may be metabolized into ketone bodies. In pure Addison's disease gluconeogenesis from protein is diminished and this may account for the lessened liability to ketosis.

Simpson[2] explains the occurrence of ketosis in his 3rd case of combined diabetes mellitus and Addison's disease by regarding the patient as not completely adrenalectomized. Baird and Munro[6] report a case in which ketosis was induced by 25 mg. of cortisone per day. Thorn and Clinton[7] suggest

that ketosis is only present when dehydration is severe, but this has not consistently been shown by others although dehydration from adrenal insufficiency, associated in part with anorexia, renders the patient more liable to ketosis. Our patient had one episode of ketosis whilst on cortisone but this could not be incriminated in the second episode since cortisone had been withheld for the previous 9 months. It is certainly true that all the recorded deaths have been in hypoglycaemia or adrenal crises and not in diabetic coma. In the management of ketosis in such cases insulin must be used cautiously in small doses and cortisone is imperative. Fluid and electrolyte therapy is much the same as for the uncomplicated diabetic coma except that potassium requirements are less.

The vascular complications of diabetes, especially those affecting the kidneys and the eyes, remain the outstanding problem in an otherwise controllable disease. It is generally accepted that the incidence of these complications increases with the duration of the disease. The possibility that some hormonal imbalance, particularly affecting the pituitary-adrenal axis, is responsible has been entertained for a few years and has at least provided a therapeutic approach. The subject has been reviewed recently[8] and it is suggested that hypophysectomy or bilateral adrenalectomy should still perhaps be considered, especially in the early stages when the changes are reversible. Our patient did not show either the kidney or eye complications such as would be expected after more than 30 years of diabetes. This is unusual but cannot be explained on the basis of his Addison's disease, which had only become apparent in the last 3—4 years.

SUMMARY

A case is presented of Addison's disease complicating a long standing diabetes mellitus. Unusual features were the development of diabetic coma and the absence of any of the late manifestations of diabetes. The role of protein metabolism in the pathogenesis of ketosis is discussed. When a well-controlled diabetic patient suddenly develops insulin sensitivity, Addison's disease, hypopituitarism, myxoedema, liver disease and congestive cardiac failure must be considered.

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