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Diabetes Mellitus Associated with Epidemic of Infectious Hepatitis in Nigeria

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British Medical Journal, 1974, **1**, 183–185

Summary

This report concerns nine cases of diabetes mellitus associated with infectious hepatitis, an epidemic of which swept through eastern Nigeria between 1970 and 1972. All the patients showed the classical symptoms and signs of diabetes. They quickly responded to treatment, and after a few months the diabetes completely disappeared. Corticosteroid-glucose tolerance tests in four patients 12 to 30 months after the remission of their diabetes were normal. Contact with the remaining five patients had been lost a few months after clinical remission of their diabetes. The infectious hepatitis virus may have damaged pancreatic islet cells to cause an acute remittant form of diabetes mellitus.

Introduction

An association between virus infections and diabetes mellitus is well documented in both animals and man. Diabetes mellitus has followed an attack of foot-and-mouth disease in cattle (Pedini *et al.*, 1902; Barboni *et al.*, 1962). The encephalomyocarditis virus is known to cause pancreatitis and islet tissue damage in mice (Craighead, 1966), in which Coxsackie B4 and B1 virus infections are also known to damage islet tissue (Burch *et al.*, 1971). In man the mumps virus has repeatedly been accused of causing diabetes melitus. Cole (1934) suggested this association in three young diabetics. Meling and Ursing (1958) reported four cases within nine months after an epidemic of mumps in Sweden, when they studied 40 children and two adults. Hinden (1962) found reports of 20 cases and reported a case of his own where severe diabetes mellitus with coma occurred in a 15-month-old child about five weeks after an attack of mumps. Conceivably, therefore, other viruses may damage the islet tissue in the pancreas of man, either temporarily or permanently, to produce clinical diabetes mellitus. Nevertheless, I have been unable to find in the English language medical literature any record of cases of diabetes mellitus associated with infectious hepatitis. This paper reports what must be the unusually large number of nine cases of this association.

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Patients

The nine patients who developed clinical diabetes mellitus after an attack of infectious hepatitis formed part of a group of about 100 cases of the disease seen by me during an epidemic which ravaged the eastern region of Nigeria from 1969 to 1971. It started in the dying stages of the Nigerian civil war, in what was then known as Biafra. An estimated seven to eight million people were crammed into a land space of about 60 by 40 miles (80 by 64 km) in what must have been the longest siege in recent history. With a breakdown in public health measures and severe overcrowding a classical epidemic of infectious hepatitis swept through a population already severely ravaged by malnutrition and starvation. This background picture might be pertinent in that the nutritional status of the patients may have played some part in the development of the diabetic complication. Nevertheless, the civil war ended in January 1970 and all the cases of diabetes reported in this paper were seen between 1970 and 1972 when nutrition had much improved.

All the nine patients presented with classical symptoms and signs of diabetes mellitus, with marked wasting and dehydration associated with polydipsia and polyuria and in some cases with ketosis. They had glycosuria and a raised fasting blood sugar. They all required insulin followed by oral hypoglycaemic therapy for some months. They then clinically remitted. Five of the cases are not reported in detail here because they defaulted from follow-up, presumably because they remained well.

During follow-up the patients tested their urine with Clinitest tablets daily for the first four to eight weeks and thereafter on three days a week. At first no sugar or glucose powder was allowed but otherwise the normal African diet of mostly carbohydrate foods such as cassava, yam, maize, and rice was unrestricted. The reason for not restricting the diet was that all the patients when first seen were wasted from both the acute liver disease, with its associated marked anorexia for protein and fatty foods, and the diabetes. On a free diet and insulin the diabetes was quickly brought under control and, since the need for insulin progressively diminished, there was no need to interfere with the usual diet. After varying periods of follow-up a modified corticosteroid-glucose tolerance test (Fajans and Conn, 1954) was done, in which each patient was given a total of 40 mg of prednisolone in four divided doses the day before he reported as an outpatient for a standard glucose-tolerance test. Blood sugars were estimated on capillary blood samples by the method of Folin and Wu.

Case 1

The patient, a 39-year-old printer, was first seen and admitted to hospital in December 1970 with polyuria, polydipsia, and loss of weight over the preceding two weeks. There was no family history of diabetes mellitus. He was taken ill in September 1970 with severe infectious hepatitis. An epidemic of jaundice had been raging in the

area where he lived at the time. Advised to take a lot of glucose, he had taken a total of 18 2·2-kg tins of glucose powder over the preceding four months. Sometime in September he had been given 5 mg of prednisolone three times a day for a week. On examination he was slightly jaundiced and moderately emaciated. The urine contained over 2% glucose but no ketone bodies. Fasting blood sugar was 250 mg/100 ml.

He was started on soluble insulin 20 U three times a day just before meals. Normal ward diet was allowed but not sugar or glucose in drinks. The diabetes was soon controlled and the insulin requirement progressively reduced. He was discharged after two weeks on chlorpropamide 500 mg daily, which was reduced to 250 mg each morning after another two weeks. All antidiabetic drugs were discontinued in February 1971. After a further 14 months, despite an unrestricted diet, he remained symptom-free and his urine sugar-free. On 15 March 1972 a corticosteroid-glucose tolerance test was normal (fig. 1). After 30 months without treatment or dieting he was well and fully at work.

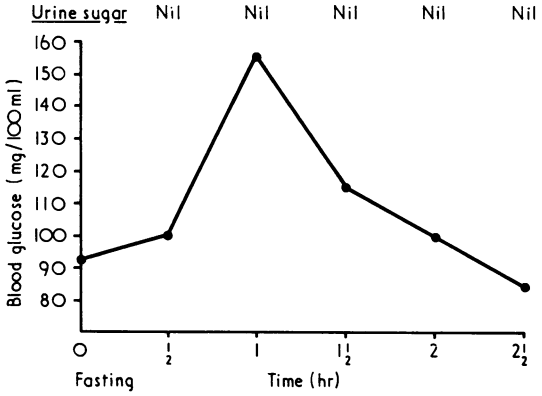

FIG. 1—Case 1. Oral glucose tolerance test after corticosteroid load and ingestion of 50 g glucose.

Case 2

The patient, a 36-year-old electrician, was first seen on 9 January 1971 complaining of severe weight loss, marked weakness, severe polyuria, and gross polydipsia for about three weeks. There was no family history of diabetes mellitus. He had not been to work since developing infectious hepatitis eight weeks previously, an epidemic of which was raging at the time. He had had prednisolone 15 mg daily for three weeks and had taken about six tins of glucose. On examination he was very emaciated, extremely weak, and grossly dehydrated. His urine contained over 2% glucose and ketone bodies. There were no facilities for emergency blood sugar estimations and he refused admission to hospital.

He was immediately given saline 3 l. intravenously and soluble insulin, and thereafter 40 U of soluble insulin twice daily as an outpatient for two weeks. This was later changed to 60 U each morning, reducing to 40 U, for a further two weeks. Treatment was continued with chlorpropamide 500 mg each morning, reducing to 250 mg, for a total period of 14 weeks. He was allowed to eat normally except for sugar. He gained weight from 113 lb (51 kg) to his usual weight of 136 lb (62 kg) and remained well and his urine sugar-free. All antidiabetic drugs were discontinued on 29 May 1971. Nine months later a corticosteroid-glucose tolerance test was normal. When seen more than two years after stopping treatment he was well and at work.

Case 3

The patient, a 47-year-old businessman, when first seen on 23 August 1971 had been ill for two weeks with malaise, vague joint pains, marked tiredness, anorexia, and dark-coloured urine. He had been treated for malaria but was not improving. He was jaundiced but otherwise looked well. His urine was free of sugar but contained much bilirubin and an excess of urobilinogen. He weighed 189 lb (86 kg). A diagnosis of infectious hepatitis was reinforced by a history of recent contact with this disease. He improved rapidly with treatment, which included prednisolone 15 mg daily for about three weeks, regaining his strength and appetite and the jaundice almost completely cleared. He thought he had recovered, but he soon began to pass urine often, drink more water, and lose weight despite a good appetite. After two weeks he again sought medical advice.

There was no family history of diabetes mellitus. He looked emaciated. His weight had dropped to 154 lb (70 kg). The urine contained more than 2% of glucose and a trace of ketones. Liver function tests showed: total bilirubin 1·4 mg/100 ml, conjugated bilirubin 0·5 mg/100 ml, thymol turbidity 4 U, and thymol flocculation negative. A glucose tolerance test the day after admission confirmed a diagnosis of clinical diabetes mellitus (fig. 2). He was treated with soluble insulin 20 U three times a day just before food and was allowed a normal ward diet, but no sugar or glucose. His diabetes was quickly controlled and his requirements soon fell below protamine zinc insulin 40 U daily. Chlorpropamide 500 mg and later 250 mg daily was substituted and he was discharged on this regimen after three weeks. He returned to his normal business. He drank no alcohol because of his recent liver disease but he ate normally. On 30 November 1971 he was quite well and weighed 180 lb (82 kg). His urine had remained free of sugar and so the chlorpropamide was stopped. After cessation of all treatment for diabetes mellitus a corticosteroid-glucose tolerance test 18 months later was normal. After 20 months follow-up the patient remained well.

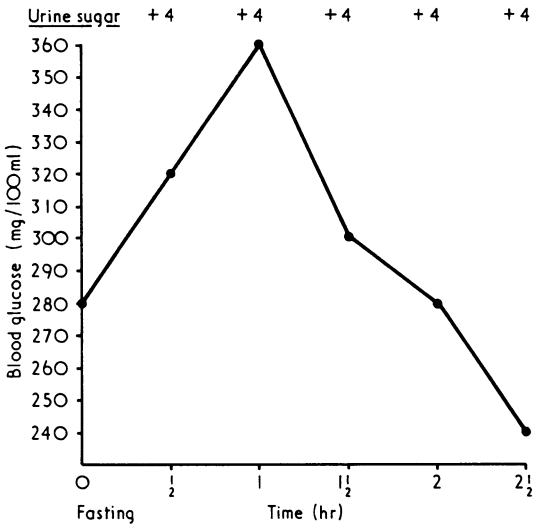

FIG. 2—Case 3. Oral glucose tolerance test after ingestion of 50 g glucose.

Case 4

The patient, a 28-year-old civil servant, was first seen on 12 May 1972. Seven weeks previously he had developed infectious hepatitis, and among other treatments he had been given prednisolone 5 mg three times a day for two weeks. His jaundice cleared but after six weeks he developed symptoms of diabetes, with glycosuria, and a fasting blood sugar of 157 mg/100 ml. He was admitted to hospital and treated along the same lines as the other patients reported above. The glycosuria soon stopped and he was discharged after ten days taking chlorpropamide 500 mg daily, which a week later was reduced to 250 mg daily. After another four weeks all antidiabetic treatment was discontinued as urine tests were consistently sugar-free. The patient had returned to work, was well, and was eating an unrestricted diet. A year later a corticosteroid-glucose tolerance test was normal, and he continued in good health.

Discussion

The aetiology of diabetes mellitus, though not fully understood, is now thought to be multifactorial, embracing heredity, insufficient production of insulin by the pancreas, over-production of other hormones, circulating insulin antagonists, and the pro-

duction of abnormal forms of insulin. The role of excessive ingestion of carbohydrate foods, which must promote a sustained demand for large amounts of insulin, has not yet been fully elucidated. The present series of cases suggests that the role of infections of the pancreas by certain viruses must be more seriously considered.

Questions that spring to mind are: Was the causative virus the one usually associated with infectious hepatitis or was it serum hepatitis? Was it a yellow fever epidemic misdiagnosed as infectious hepatitis? Was it a true infectious hepatitis but caused by a virus of a different strain from the one that causes the disease in other parts of the world? I am certain that the cases of epidemic jaundice were clinically indistinguishable from the classical textbook description of acute infectious hepatitis, and, apart from being particularly severe, and fatal in many cases, resembled the sporadic cases of infectious hepatitis we see often in the tropics. The possibility of yellow fever was considered, but a World Health Organization expert, invited by the State Ministry of Health to look into the matter, found no evidence of yellow fever virus as the cause. One wonders whether the diabetes mellitus developed as a result of the stress of the infection or whether the patients had potential or latent diabetes which illness or the injudicious use of steroids made manifest. Possibly the virus that caused the hepatitis also affected the pancreas, preventing it from producing enough insulin. Or it could be that the insulin stores in the pancreas were temporarily exhausted by the prolonged demand of a high carbohydrate or glucose intake.

That these were merely episodes of diabetes in potential or latent diabetics is unlikely, because none of the patients had a family history of diabetes and no previous history of a diabetic episode. Moreover, corticosteroid-glucose tolerance tests failed to show any abnormality in any of them. Neither can stress of infection be held primarily responsible, for the diabetic symptoms invariably appeared several weeks after the onset of the jaundice and usually as the patients were recovering. Thus the peak of the stress of the infectious hepatitis was much earlier than the time of onset of the diabetes. The diabetes is unlikely to have been due to the prednisolone given to some of the patients. The dose never exceeded 15 mg daily; it was given for not more than three weeks; and, apart from case 3, the diabetic symptoms appeared after prednisolone had been stopped. Moreover, none of the patients showed glycosuria or any abnormality in the corticosteroid-glucose tolerance test after recovery.

We are therefore left with two possibilities—namely, that the capacity of the pancreas to produce enough insulin was temporarily exhausted by the stimulus of a sustained high carbohydrate or glucose intake, or that it was diminished by virus infection. Many laymen in Nigeria think diabetes mellitus is caused by eating too much sugar. The history given by the patient in case 1 that he had taken a total of 39·6 kg of pure glucose in the four months before his diabetic symptoms began made me reflect on the possible contributory role of the diet in the aetiology of diabetes. Diabetes mellitus is quite common in the tropics. Its exact prevalence in the Nigerian population is not known, but it would be interesting to compare the prevalence in the far north of the country, where a high protein diet is eaten, with that in eastern states where the carbohydrate intake is high and the protein intake low. Seltzer and Harris (1964) maintained a prolonged stimulation of the pancreas by infusing glucose intravenously for seven days in normal persons, in mild diabetics, and in elderly insulin-dependent diabetics. The normal people showed greatly increased plasma insulin levels, retained all the infused glucose, and showed no hyperglycaemia. The mild diabetics showed an intermediate response, but the elderly patients showed a more pronounced and more persistent hyperglycaemia and glycosuria and their plasma insulin levels rose for only the first two days and then fell almost to zero. Thus it is possible under certain circumstances to stimulate pancreatic insulin secretion to a point of exhaustion.

Turning lastly to the possibility of virus infection of the pancreas itself, there is abundant evidence in both animals and man that certain viruses can cause diabetes mellitus (Pedini *et al.*, 1902; Craighead, 1966; Cole, 1934; Meling and Ursing, 1958; and Hinden, 1962). My clinical observations suggest that the virus of acute infectious hepatitis may also damage the pancreas to produce an acute remittent form of clinical diabetes mellitus. The possibility that in some other patients this damage be more permanent cannot be ruled out. The work of Martin and Lacey (1963) on the production of diabetes by partial pancreatectomy in the rat could explain why the diabetes in the present series of patients tended to appear several weeks after the peak of the infectious hepatitis. Martin and Lacey found that after removing 95% of the pancreas there was a prediabetic period of about three weeks before the diabetic phase. In cases of diabetes mellitus in man after infection by the mumps virus this prediabetic period has also been noted. It has sometimes lasted for as long as nine months. Obviously more research is needed to unravel some of the mysteries still surrounding the aetiology of diabetes mellitus, particularly that of the role of viruses in causing the disease in man.

I wish to thank Dr. M. Ezeama for referring one of the patients, and Mr. L. O. U. Agu for secretarial assistance.

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