Malnutrition-related Diabetes Mellitus in Africa

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INTRODUCTION

Diabetes mellitus was thought to be rare in Africans up to the 1930's and even up to the sixties in some countries [1]. However, subsequent hospital-based observations have confirmed that it is not uncommon. Both Type 1 and Type 2 diabetes are seen, the latter being much more common. More recently, an apparent increase in the incidence of Type 2 has been observed in association with the adoption of a 'Western lifestyle' among the new and expanding class of urban elite.

In addition to Type 1 and Type 2 diabetes, cases not easily fitting into these types have been described from many countries in sub Saharan Africa. Prominent among these are the 2 sub types of what has been designated malnutrition- related diabetes mellitus (MRDM) by the WHO [2]: the fibrocalcific or fibrocalculous pancreatic diabetes (FCPD) and the protein-deficient pancreatic diabetes (PDPD) (also referred to as protein-deficient diabetes mellitus (PDDM)). Less commonly reported variants include non-insulin-dependent diabetes of the young [3], temporary diabetes [4] and intermittent insulin-dependent - diabetes [5].

This review deals with a survey of information pertaining to MRDM. Clinical diagnostic criteria for FCPD and PDPD will not be discussed in - detail because they have already been extensively covered in several papers [6,7,8]. Basically FCPD is characterised by a socioeconomic setting of poverty and malnutrition, onset in youth (commonly below the age of 30 years), clinical evidence of malnutrition, insulin-requirement for - control, ketosis-resistance, and radiologically demonstrable pancreatic calcification and/or evidence of exocrine pancreatic dysfunction. PDPD (previously referred to as J-type) has many of the same characteristics but differs from FCPD in absence of clinical and radiological evidence of pancreatic dysfunction and relative resistance to insulin. But these characteristics are not uniformly present in patients in either category and cohorts described from some countries exhibit important differences from the two better recognized subtypes of MRDM (as described later) which suggest heterogeneity of both FCPD and PDPD.

PREVALENCE

Population surveys using various diagnostic criteria for diabetes show a lower prevalence than in developed countries. None have found a convincing causal association between malnutrition and diabetes. Peters [9] in Gondar, northwest Ethiopia, found an overall prevalence of 0.3 percent with an increase to 2.4 per cent in the small number of subjects above 40 years of age. Imperato et al [10] and Fisch et al [11] in Mali found that diabetes was less common than in Western countries. In relation to race, occupation and dietary habits it was more common in caucasoids than in negroids, in the pastoralists and sedentary groups (merchants and civil servants) than in peasants who also consumed more carbohydrate and were physically more active than the former two groups. In relation to age and nutritional status prevalence was more common in the obese and older age groups similar to the well known pattern in Western countries. Thus no association was observed between malnutrition and diabetes in this Sahelian country which is subject to repeated droughts and famine. But Cohen et al [12] who conducted an oral glucose tolerance test in 158 young Ethiopian Jews who had been in Israel for 2.5 to 4 years found a surprisingly high prevalence of 8.9 per cent. The immigrants came from an impoverished rural environment in northwestern Ethiopia where they had subsisted on a meagre diet of carbohydrate and vegetables similar to that of our MRDM patients [13]. There fore, the high diabetes prevalence could at first suggest an association with chronic malnutrition. However, a later study by Rubinstein et al [14] on newly arrived Ethiopians showed a prevalence of only 0.4 per cent. This is similar to the finding by Peters [9] in the geographic area of origin of the Ethiopian Jews in a population generally sharing the same genetic background with them. The high prevalence in the earlier study has been ascribed to abrupt exposure of the subjects to a Western life-style and the related high energy, high fat, refined carbohydrate diet (together with a reduc-tion in physical activity) in their new environment. The unexpectedly high frequency of diabetes in them could therefore reflect the disadvantage of the 'thrifty genotype' in an environment of plenty [15] rather than a causal association with previous malnutrition.

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Teuscher et al [16] in a survey of diabetes prevalence in 2 rural villages in Togo with a high cassava/carbohydrate consumption found no positive correlation with either a low BMI or cassava consumption. In fact, they ascribed this low prevalence to the protective effect of the high carbohydrate diet. McLarty et al [17] in a survey covering 6 villages in Tanzania applied WHO criteria for the diagnosis of diabetes and BMI levels for classifying the subjects into underweight ($\leq$20 kg/m^2), normal weight (20-25 kg/m^2) and overweight ($\geq$25 kg/m^2). They found an overall prevalence rate of 0.9% which was lower than in developed countries and a Ushaped pattern in relation to nutritional status (higher in the under and overweight than in the normal weight group). But the rise in blood glucose in the underweight was small in absolute terms. A more recent study by the same group [18] found no consistent relation between low BMI or cassava consumption and diabetes prevalence.

CLINICAL OBSERVATIONS

The report by Shaper [19] from Uganda was among the first on MRDM from Subsaharan Africa. Common findings in the patients were softening and redness of the hair, parotid enlargement, steatorrhoea and radiologically demonstrable pancreatic calcification. They required insulin for control in conventional doses and showed susceptibility to both ketoacidosis and hypoglycaemia. This variant which belongs to the FCPD subtype has subsequently been described from many other African countries. The clinical descriptions and ancillary investigations show many common features but certain other aspects such as the relation of pancreatic disease to alcohol consumption and the significance of abdominal pain or a past history of it as evidence of chronic pancreatic disease are more variable [20, 21]. However, although alcohol could have relevance to the problem in adults, it is not seriously considered as having an aetiological role in children and adolescents [22].

The proportion of patients assigned to primary diabetes (Type 1 and Type 2) and MRDM varies between countries. Osuntokun et al [23] found FCPD in 8.6 per cent of 832 patients but did not mention the J-type (PDPD) in their report, Akanji [24] reported 6 per cent as falling into the MRDM category, Kajubi [25] estimated 7-8 per cent at Mulago Hospital in Uganda to be of the pancreatic type. Castle and Wicks in Harare, Zimbabwe [22] found 23 per cent of 93 patients to be of the pancreatic type but such a high figure is exceptional in African series. This is in contrast to the situation in South India for which figures as high as 70 per cent have been quoted in some reviews [6]. An additional peculiarity that is obvious is the variation in the proportion of patients assigned to Type 1, Type 2 and MRDM at difierent times and by different observers in the same geographic locations. This is particularly evident in relation to the insulin-requiring, ketosis-resistant cases without pancreatic calcification which have been variously included in Type 1, Type 2 or PDPD (J-type in earlier reports). In other instances, no classification has been offered [26]. In Ethiopia, cases generally conforming with PDPD type, except for their response to conventional doses of insulin, constituted 74 per cent of 94 diabetic patients reported by Belcher from Gondar [27]. The author designated this category 'Intermediate diabetes' (i.e. between Type 1 and Type 2) in consideration of the two major clinical characteristics (insulinrequirement for diabetic control on the one hand and resistance to ketoacidosis on insulin interruption on the other). Subsequently Peters [28] saw no convincing clinical characteristics warranting consideration of MRDM as a separate category in patients from the same geographic and socioeconomic environment and felt that the characteristics described earlier by Belcher [28] were not by themselves indicative of a different type of diabetes.

The gender pattern generally shows a preponderance of males. But this may not reflect the real situation because the pattern of hospital medical admissions also often shows a similar pattern. The male bias may therefore be related to cultural , geographic and socioeconomic factors rather than the gender-related prevalence of MRDM. However, where alcohol has an important role in pancreatic disease in adults such as in Zimbabwe [22] the male preponderance could be a more genuine indicator of the higher prevalence of FCPD in males.

An intriguing finding in relation to MRDM in females at our clinic is the proportion of those in childbearing age who have successfully carried their pregnancies to a normal full term delivery at home despite poor diabetic control and interruption of follow-up altogether during most of the gestation period. However, the total number of females in the MRDM group is too small to justify any inferences from this observation.

COMPLICATIONS

The duration of follow-up is less than 5 years for the majority of our MRDM patients. This is related to the complex problems associated with an incurable disease in an environment of extreme

poverty. The cost of transportation and the difficulties with dietary control for most of the patients who live in a situation of marginal food availability and marked seasonal variations, the need for daily insulin injections and the precarious supply of insulin often defeat the will to persevere. They are frequently tempted or advised by relatives and neighbours to seek alternative remedies such as holy water or herbal medicines. In other cases the terminal event is related to the supervention of a fatal acute illness at home. Thus only 20 (32 per cent) of the 63 patients first seen during our nutritional rehabilitation study 6 to 7 years ago are still continuing their follow-up with us. Of the remainder 4 are known to have died outside hospital and 2 others had been referred to provincial hospitals nearer their home. No information is available on the fate of the rest.

Acute complications

In our series, pyogenic and fungal infections, scabies (which often covers the whole skin surface in the severely debilitated), and pulmonary tuberculosis are common. Hypoglycaemia which was reported to be an important cause of death in Ugandan patients [25] is seen in our patients but no deaths have occurred from it in hospital in the last 10 years. Periodontitis leading to premature loss of teeth is almost universal among our patients followed for 5 years or more.

Chronic complications

Neuropathy is common even at first presentation. Painful neuropathy was seen almost exclusively in the MRDM category during the nutritional rehabilitation studies [29]. It started during treatment in almost all cases, involved the whole body in those most severely affected and was incapacitating to the extent of interfering with eating and sleep. It was difficult to relieve and lasted for several months. Cataract developed in a few patients within the first 10 years of diabetes. Retinopathy and nephropathy are rare but this has to be seen in the light of the relatively short duration of follow-up in the majority of cases because these complications are seen in Indian patients followed for long periods. The rarity of macrovascular complications however is probably related to the restriction of MRDM to those below the age of 40 years and the short life expectancy after the onset of diabetes which is in turn related to inadequate control and frequency of fatal acute complications.

Causes of Death

In our cases the immediate causes related to diabetes are overwhelming infection, ketoacidosis in those who have been under follow-up for some years. This agrees with reports from other centres. Renal failure due to diabetic nephropathy and deaths due to macrovascular disease are insignificant because of the relatively short life-expectancy of these patients after development of diabetes. But the fate of a lot of patients who are lost to follow-up is unknown.

PATHOLOGY

In FCPD the pancreas is shrunken and shows extensive fibrosis involving the acinar and islet tissues [30]. There is no evidence of inflammation. The ducts are dilated and calculi are confined to the ducts. In cases without calcification the pancreas shows fibrosis in the same pattern as in those with calculi but the dilated ducts contain inspissated material and concretions without calcium.

Pathology reports are less common in PDPD. In 2 cases at our hospital [29] one showed a markedly shrunken fibrotic pancreas without calculi while the other case showed polymorphonuclear and mononuclear inflammatory cell infiltration in addition to extensive fibrosis.

PATHOPHYSIOLOGICAL AND AETIOLOGICAL CONSIDERATIONS

The aetiology of MRDM remains controversial. Clinical observations indicate that both FCPD and PDPD occur in poor populations. The patients are commonly less than 40 years of age, are underweight or cachectic and exhibit hair and skin changes and parotid enlargement typical of severe malnutrition. Since many patients first present months or years after the onset of symptoms, at least part of the malnutrition may be secondary to the diabetes and, in this respect, Lester's finding that 50 per cent of the patients whose BMI was less than 18 kg/m^2 at first presentation had a normal prediabetic weight is worthy of note [31]. However, a large percentage of our patients come from rural communities where malnutrition is common [32, 33].

The majority of patients (both FCPD and PDPD) come from environments in which food supply is chronically inadequate and deficient in essential nutrients. Cyanide toxicity from cassava consumption had been invoked as a possible cause but a number of studies have failed to show a convincing relationship [16,18]. Furthermore, MRDM also occurs outside cassava staple areas. Cassava is virtually unknown in Ethiopia but another starchy root, *Ensete ventricosum*, which is poor in protein and micronutrients [34,35],

together with cabbage constitute the staple food item of poor peasants in an area where a significant proportion of our typically malnourished diabetic patients come from.

The majority of MRDM patients require insulin for control (conventional doses in FCPD, large doses in PDPD) but are generally ketosis-resistant on insulin interruption. Abdominal pain in the FCPD type is variously described as common and characteristic [25] or infrequent and unremarkable [36] by different observers. Ketoacidosis although not found in the majority is not rare even in confirmed FCPD types as in the series by Osuntokun et al [23]. Although the majority in most series have been found to require insulin for control, a significant proportion respond to oral agents. Morley et al [36] found that 10 of 21 patients fitting into the MRDM category among a total of 170 diabetic patients responded to oral agents. Therefore, in terms of insulin requirement for control as well as in ketosis-proneness MRDM patients are not a homogeneous category. In our series studied during a period of nutritional rehabilitation, ketosis or frank ketoacidosis occurred within 6 days of insulin withdrawal in 6 of 21 patients who first came to hospital from 3 months to one year or more after the onset of diabetic symptoms. The difference in their clinical status between initial presentation and the time of insulin withdrawal was the significant weight gain during the 6 to 8 weeks of nutritional rehabilitation. Longterm follow-up of Jamaican patients who showed clinical characteristics of MRDM at diagnosis revealed that a significant proportion of those who exhibited insulin resistance became responsive to conventional doses [37] and ketosis-resistance was replaced by ketosisproneness. In addition, during nutritional rehabilitation, some patients who had been ketosis-resistant for months initially had shown ketosis proneness within one week of insulin interruption after nutritional rehabilitation [29]. These findings suggest that, in the malnourished state, low body fat limiting the availability of free fatty acids as susbstrate for ketone production may mitigate development of ketoacidosis.

In the case of FCPD, clinical manifestations of pancreatic disease, characteristic abdominal pain or a past history of it, steatorrhoea and radiological evidence of pancreatic calcification or ultrasound signs of ductal dilatation favour pancreatic disease as the cause of the diabetes. The variable association between exocrine pancreatic dysfunction and diabetes and the spectrum of clinical characteristics of the diabetes itself from ketosis proneness at one end to oral agent responsiveness at the other suggest aetiologic heterogeneity [25,38]. But a careful comparison of exocrine pancreatic and B cell functions in FCPD patients in comparison with non-diabetic individuals with tropical calcific pancreatitis has demonstrated a close correlation between the severity of B cell loss and the exocrine dysfunction [40]. These findings favour a common pancreatic aetiology for the tropical pancreatic-endocrine problem to which FCPD belongs. Although heavy alcohol consumption is thought to have a contributory role in the pancreatic damage in older patients in Africa [22,40] it is not considered important in the case of children and adolescents with FCPD where the cause of the pancreatic disease remain.s undetermined.

The aetiology of PDPD is more controversial. To begin with the clinical characteristics do not show a clear demarcation particularly from Type 1 diabetes. The salient features are evidence of chronic malnutrition and a long history of the classical symptoms of diabetes at first presentation. Survival for months or years without treatment after onset of diabetes immediately suggests resistance to ketoacidosis. Ketosis resistance is also seen subsequently on insulin interruption. However, susceptibility to ketosis is seen in a significant percentage of patients followed for some years [31] or even within a short period of time after nutritional rehabilitation [30].

It is widely held that exocrine pancreatic abnormality is not a feature of PDPD. However, during one of our studies [29], 3 patients had steatorrhoea initially and 14 of 30 patients below the age of 40 years had excess stool fat not attributable to intestinal parasites. The malabsorption resolved during nutritional rehabilitation. Therefore, the pancreatic abnormality was thought to be due to malnutrition (as in kwashiorkor) aggravated by the superimposed diabetes. In any case exocrine pancreatic deficiency is not specific to malnutrition-related diabetes because it also occurs in both Type 1 and Type 2 diabetes [41,42]. But pancreatic calcification and malabsorption have not been described in either type of primary diabetes.

Concerning hormonal patterns, basal and stimulated C-peptide and glucagon profiles were not significantly different from Type 1 in our cases [29]. However, separation of patients into keotosis-prone, insulin-requiring but ketosis-resistant and oral agent responsive has shown C-peptide patterns commensurate with these clinical characteristics. Kajubi found low growth hormone levels in Ugandan FCPD cases [25]. These findings and studies of hormonal patterns and

lipid substrate dynamics from India which have shown absence oi a paradoxical rise in glucagon during OGTT and inhibition of lipolysis during insulin withdrawal go some way towards explaining the mechanisms for the ketosis-resistance in MRDM but cannot by themselves elucidate the aetiology of the diabetes.

HLA studies are few. Our study of cases which generally fit into the PDPD category [43] showed a DR3 frequency comparable to that in Type 1 [44]. Interestingly, some European studies [45] have shown a preferential association of DR3 with a milder variant of Type 1 with a lower susceptibility to ketoacidosis and found more commonly in older children. Islet cell antibody (ICA) was positive in 7 of 21 MRDM cases unselected for duration of diabetes (unpublished data). But it should be noted that ICA has been shown to be uncommon in some other African countries and populations of African origin or could not differentiate between Type 1 and Type 2 [46,47]. This demonstrates that in such studies an essential prerequisite is that the patients have to be from the same racial group for a meaningful interpretation of the results.

Recently, a study of the HLA pattern in South Indian MRDM patients with clinical characteristics identical with our MRDM has shown a predominance of DR7, DQw9 [48]. This differed significantly from the high frequency of DRw17, DQw2 found in Type 1 in the same population. As described above, we had found no significant difference in the HLA patterns in Type 1 and MRDM in Ethiopian patients.

CONCLUSION

In attempting to resolve these conflicting findings it may be reasonable to consider the aetiology of MRDM in the context of the still evolving and expanding view of diabetes as a syndrome resulting from a variety and variable combinations of causes some of which occur across diverse genetic and environmental settings while others are found only in narrowly circumscribed areas. The ubiquity of HLA DR3 and/or DR4 in association with Type 1 diabetes is an example of the former and the restriction of HLA A2 in Type 2 diabetes to the Xhosa of South Africa of the latter [49]. The application of clinical characteristics alone as indicators of the underlying aetiology and as criteria for classification have serious limitations. Thus although susceptibility to ketoacidosis is accepted as a hallmark of Type 1 diabetes, even in Western countries, resistance to it is not a rare phenomenon as exemplified by patients who survived for a number of years on the Allen diet before the insulin era [50]. Conversely, the development of frank ketoacidosis in typical Type 2 patients in certain situations of acute stress is well-known. Concerning the cause of B cell destruction in Type 1 diabetes, although it is commonly postulated that the environmental trigger is viral infection, the evidence is still not conclusive. In relation to the HLA pattern in Type 1 diabetes, in contrast to the finding in caucasoids, the protective role of aspartate DQβ-57 has not been corroborated in Japanese patients. Another phenomenon worthy of note is that found in a minority of adults with Type 2 diabetes who develop insulin dependence within a few years of the diagnosis of diabetes. HLA & ICA studies have shown evidence in favour of Type I diabetes in these cases [51,52]. And more recently Zimmet [53] has advanced the view that some patients now classified as Type 2 on the basis of commonly accepted criteria might in fact belong to a subclass of Type 1. Therefore, in keeping with this expansion in the concept of the aetiology of diabetes it is also possible that in the case of MRDM we may be dealing with a spectrum of aetiologies encompassing variable combinations of genetic and environmental factors in some areas and predominantly environmental causes in other areas. The clinical manifestations would be expected to have correspondingly varying features. Comparison of the HLA patterns in MRDM in our series [43] and a group in the same category in South India [48] provides an illustrative example. The clinical features in the two groups were identical. But, as described earlier, while our cases showed HLA patterns similar to Type 1, those in South India had no alleles commonly associated with Type 1 .

The findings from various countries indicate that in order to resolve the question of the aetiology of MRDM, HLA and B cell auto-antibody studies would be valuable but only if appropriately matched Type 1 and Type 2 subjects in the same population are used as controls. The answer to the question of the temporal relationship between malnutrition and diabetes can be best answered by longitudinal community-based studies of the natural history of diabetes in areas where MRDM occurs. In addition, the role of nutritional deficiencies, particularly essential amino acids, certain minerals and vitamins, in relation to B cell life and function also needs to be addressed comprehensively [54].

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