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Letters to the Editor

Tropical malnutrition diabetes

Dear Sir,

I write to comment on the article by Mohan et al. [1] that calls attention to the similarities and differences between diabetes occurring in the tropics and diabetes in temperate regions. I find that the report contains many facts of interest and makes several new points, but I would like to take issue with two of its assertions. My first concern is with the authors' apparent blending of one or both forms of diabetes seen in the temperate zone (Types 1 and 2) with a form unique to the tropics and clearly associated with gross undernutrition. Their presumed mixing of different types reduces the report's value.

Discussion at a session on tropical diabetes at the September 1985 IDF meeting in Madrid pointed out the need for a useful working definition of the form of diabetes that Geevarghese and I referred to as tropical malnutrition diabetes [2]. I suggest that two major (necessary) criteria and three minor (supportive) criteria be used in identifying the cases. The first major criterion is geographic; the disorder should develop in a person living between the Tropic of Cancer and the Tropic of Capricorn. The second major criterion is that chronic low protein and low calorie intake be present. Dietary protein should be below 35 (perhaps even 30) grams per day and body weight should be well below ideal. Supportive physical findings are impaired muscle mass and tone, parotid enlargement, and skin and hair disruption and color changes.

The first minor criterion is evidence of exocrine pancreatic disease. This is most commonly recognized as the presence of stones in the pancreatic ducts and antecedent or associated abdominal pain. Ahuja has informed me that ultrasonic examination has revealed radiologically unrecognized pancreatic stones in patients in Northern India, where this association was rarely identified before.

The second minor criterion is the need for insulin in management. Physicians treating this disorder regularly indicate that large doses are required to normalize the blood glucose level. In contrast with Type 1 diabetes, insulin is used to avert inanition, not ketoacidosis.

The third minor criterion is onset in adolescence or early adult life. While this is common in most tropical countries, there is evidence that an African form associated with Kaffir beer ingestion develops after age 30.

The low frequency of insulin use and near absence of severe nutritional disturbance suggest a contribution by Type 2 diabetes to the pancreatic diabetes group reported by Mohan et al. [1]. It would be very useful if future reports detailed the number of criteria met in each study to allow more effective comparisons.

The second issue that I would like to raise is the authors' challenge to the cyanide ingestion hypothesis. Mohan et al. [1] argue that failure to consume cassava (a crop grown in India only in Kerala state) argues against the cyanide hypothesis. While we have pointed out a strong relation between cassava consumption and tropical malnutrition diabetes on a worldwide basis [2], the existence of the disorder outside of cassava-consuming areas in India was recognized. In at least two regions of India the regular use of another cyanide-containing food, ragi, has been documented. In Belgaum (Karnataka state), Dr. S.J. Nagalotimath has written me about the relationship, while near Cuttack (Orissa state), B.B. Tripathy has told me of its regular use in gruel by individuals developing the disorder there. In addition to ragi, two other food sources likely to contain cyanide are consumed widely in India. Jowar, the Indian name for sorghum (milo), is consumed in the North. Peas are a major protein food in Tamil Nadu state, the source of the report of Mohan et al. [1]. More exact information about the diets of the diabetic subjects meeting the two major criteria and one or more minor criteria would be very helpful in future examinations of the cyanide hypothesis. It should be noted by those who have contact with the disorder in Africa that it is likely that at least some Kaffir beers contain non-lethal amounts of cyanide.

To understand the potential adverse consequences of nonlethal cyanide ingestion, it is useful to point out its effect on sulfur amino acid availability. A vigorous cyanide detoxification mechanism uses thiosulfate generated from cysteine as the sulfur source [3]. Similar detoxification reactions not using thiosulfate all require sulfur arising from cysteine and methionine, and they also generate thiocyanate, a goitrogen slowly excreted in the urine [4]. We have shown recently that cyanide not destroyed by either mechanism still attacks sulfur atoms in protein molecules [5].

The attack of cyanide on disulfide bonds in protein molecules has been shown to lead to the formation of 2-imino-4-thiazolidinecarboxylic acid [6], also excreted in the urine. This difference in fate suggests that a simple urine test for cyanide-mediated tropical malnutrition diabetes could be measurement of the ratio of 2-imino-4-thiazolidinecarboxylic acid to thiocyanate in newly diagnosed cases and in risk populations.

My last comments underline an aspect of cyanide ingestion that has wide nutritional importance even if the cyanide hypothesis is incorrect. The ingestion (or inhalation) of small amounts of cyanide is both common and detrimental to protein nutrition. It always robs the body of a stoichiometric amount of sulfur, burdening the individual's nutrition, especially skin and hair formation. In the tropics, where protein intake is lower than in the temperate zone for reasons linked as much to calorigenesis as to economics, the need to avoid reduced availability of essential amino acids has very special importance. In the case of cyanide, there is reason to believe that simple alternatives in food preparation could solve the ingestion problem.

Very truly yours,
Donald E. McMillan, M.D.

References

1. Mohan V, Mohan R, Susheela L, Snehalatha C, Bharani G, Mahajan VK, Ramachandran A, Viswanathan M, Kohner EM (1985) Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetologia 28: 229-232
2. McMillan DE, Geevarghese PJ (1979) Dietary cyanide and tropical malnutrition diabetes. Diabetes Care 2: 202-208
3. Weng L, Heinrikson RL, Westley J (1978) Active site cysteinyl and arginyl residues of rhodanese: A novel formation of disulfide bonds in the active site promoted by phenylglyoxal. J Biol Chem 253: 8109-8119
4. Sorbo B (1962) Enzymatic conversion of cyanide to thiocyanate. Proceedings of First International Pharmacological Meeting 6: 121-128
5. McMillan DE, Svoboda AC (1982) The role of erythrocytes in cyanide detoxification. J Pharmacol Exp Ther 221: 37-42
6. Wood JL, Cooley SL (1956) Detoxication of Cyanide by Cystine. J Biol Chem 218: 449-457

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Reply from the authors

Dear Sir,

We would like to reply to the two letters regarding our article on tropical pancreatic diabetes [1], one by Ahuja [2] and the other by McMillan (this issue). The first point raised by both authors concerns the diagnosis of tropical pancreatic diabetes.

It is evident from the differences in criteria recommended in the two letters that there is as yet no precise definition for the diagnosis of this form(s) of diabetes. The 1985 WHO study group on diabetes has classified malnutrition-related diabetes mellitus (MRDM) as a separate entity [3]. Under this category, two subtypes were included: fibrocalculous pancreatic diabetes and protein-deficient pancreatic diabetes. However, at present it is not clear whether these two entities represent two separate diseases or different stages of the same disease. We share the concern of Drs. Ahuja and McMillan about criteria for diagnosis of malnutrition-related diabetes mellitus. In South India, we have reported on the classical form of this type of diabetes, which is associated with malnutrition, fibrosis and/or calcification in the pancreas, exocrine pancreatic insufficiency and usually severe insulin-dependent but ketosis-resistant diabetes [4, 5]. Pancreatic biopsy and autopsy studies have shown evidence of pancreatic fibrosis in these patients [5, 6].

We define tropical pancreatic diabetes as being present in a patient in whom all of the following criteria are fulfilled:

1. Overt diabetes mellitus in a patient living in tropical countries.
2. Onset of diabetes mellitus at a young age (usually 15 to 35 years).
3. History of recurrent abdominal pain dating back to childhood
4. Evidence of extensive pancreatic calcification on plain X-ray of the abdomen and respective morphological changes in the pancreas demonstrated by ultrasonography.
5. Absence of alcoholism and other known causes of chronic pancreatitis.

Using the above criteria we recently characterized a group of patients who showed a heterogenous pattern [1]. While many required insulin therapy, some responded to oral agents. Contrary to earlier reports [4, 7], malnutrition was not a prominant feature in many of these patients. A point raised by Drs. Ahuja and McMillan in response to our article [1] is that some of our patients could possibly have had Type 2 (non-insulin-dependent) diabetes and not tropical pancreatic diabetes. We are able to justify our diagnosis of tropical pancreatic diabetes on the following grounds. Firstly, all of our patients had evidence of extensive pancreatic calcification. In the same group of patients, we recently demonstrated changes by ultrasonography in the pancreas including fibrosis and shrinkage of the gland, irregular gland margins, ductal dilatation and intraacinar or intra-ductal calculi [8]. We are not aware of any report which shows that Type 2 diabetic patients have any of the above features. Secondly, the prevalence of diabetes in India varies between 1.5 to 2% (Type 1 and Type 2 included). There is no epidemological data on the prevalence of tropical pancreatitis. However, based on clinical reports from different institutions, we can reasonably assume that it is a rare disease, at least in Madras. In view of this, it is extremely unlikely that there is a significant overlap between tropical pancreatitis (without diabetes) and Type 1 or Type 2 diabetes. Thirdly, in the absence of specific genetic markers for Type 2 diabetes it is at present impossible to distinguish between a patient with tropical pancreatic diabetes and a Type 2 diabetic patient who might have associated pancreatic calcification (but in whom the latter is not the cause of the diabetes). However, there is no justification in doing routine pancreatic biopsy because of ethical considerations. In addition, histopathological findings in the pancreas are not pathognomonic of the disease (alcoholic pancreatitis produces similar findings).

The suggestion that only insulin-treated patients or those with definitive malnutrition be included under this form of diabetes is difficult to accept. The experience from Kerala, India [9] supports our view that some of these patients do respond to oral hypoglycaemic agents. It is feasible that, in a disease presumably due to degenerative and/or toxic factors in some patients (perhaps those with better nutritional profiles), the disease may take a more protracted course. Thus, positive response to oral agents, especially in early stages of the disease, might be expected. With the improvement of nutritional standards in India, changes in the clinical presentation of the disease are not surprising. Dr. Mathew Roy of Trivandrum informs us that today many patients with tropical pancreatic diabetes in Kerala do not present with overt malnutrition as in previous years, and, indeed, some appear to have optimal nourishment (personal communication). The aim of our paper was to point out that, in a search for causative factors, it is necessary to look at the problem from a broader viewpoint instead of confining ourselves to cases with overt malnutrition. The only two consistent features of the disease are:

a) that its occurence is confined to tropical countries and
b) that fibrosis and/or calcification can be demonstrated in the pancreas.

Hence, we proposed the term 'tropical pancreatic diabetes' for this disease.

We feel that diagnosis of the non-calcific variety is fraught with further problems. The criteria commonly suggested are: BMI < 19, the ketosis - resistant nature of the diabetes and the requirement of large doses of insulin, all of which are non-specific. Since Type 1 diabetes can also occur in a malnourished individual, BMI does not have much significance as a diagnostic criterion. It is now generally known that overt ketoacidosis need not necessarily be present in every Type 1 patient; in some patients, the disease can have a subacute onset and a slower rate of destruction of B cells. Finally, not all authors agree about the requirement of large doses of insulin as a criterion [4, 9]. In many cases this may relate to the use of more impure forms of insulin in tropical countries.

Concerning the cyanide hypothesis, we agree with McMillan that foodstuffs other than cassava need to be analysed for possible toxic factors. To date, however, there is no evidence for this and it is obviously an area for future work. Serum C-peptide determinations are generally accepted on a valuable investigational tool to follow the natural history of the diabetic disease (1, 10). Finally, we could not agree more with the recommendations of the WHO study group on diabetes that "further epidemological, clinical and basic investigations are still urgently needed" (3) in the tropical form(s) of diabetes mellitus.

Yours sincerely,
V. Mohan, A. Ramachandran and M. Viswanathan

References

1. Mohan V, Mohan R, Susheela L, Snehalatha C, Bharani G, Mahajan VK, Ramachandran A, Viswanathan M, Kohner EM (1985) Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetologia 28: 229-232
2. Ahuja MMS (1985) Heterogeneity in tropical pancreatic diabetes. Diabetologia 28: 708 (letter)
3. WHO study group on Diabetes (1985) Technical report series 727, Geneva
4. Viswanathan M, Sampath KS, Sarada S, Krishnaswami CV (1973) Etiopathological and clinical angle of pancreatic diabetes from Madras J Assoc Phys Ind 21: 753-759
5. Viswanathan M (1980) Pancreatic Diabetes in India. An overview. In: Podolsky S Viswanathan M (eds) Secondary diabetes. Raven Press, New York, pp 105-116
6. Nagalotimath SJ (1985) Pancreatic pathology in pancreatic calcification with diabetes. In: Podolsky S, Viswanathan M (eds) Secondary diabetes, Raven Press, New York, 1981, pp 117-145
7. Geevarghese PJ (1968) Pancreatic diabetes. Popular prakashan, Bombay pp 110-115
8. Mohan V, Sreeram D, Ramachandran A, Viswanathan M, Doraiswamy KR (1985) Ultrasonography evaluation of the pancreas in tropical pancreatic diabetes. Acta Diabetologia Latina 22: 143-148
9. Ramachandran M, Pai KN (1977) Clinical features and management of pancreatic diabetes. In: Rao MB (ed) Diabetes Mellitus. Arnold Heimann, New Delhi, pp 239-246
10. Mohan V, Snehalatha C, Ramachandran A, Jayashree R, Viswanathan M (1983) Pancreatic beta cell function in tropical pancreatic diabetes. Metabolism 32: 1091-1092

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