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Carbohyrate tolerance in patients with tropical ataxic neuropathy — A human model of chronic cyanide intoxication

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Summary

Patients with tropical ataxic neuropathy (TAN) have been shown to have chronic cyanide intoxication. Glucose tolerance test data in a group of 88 patients with TAN and 88 matched controls who were studied several years ago were analysed. A standard glucose tolerance test (SGTT) with 50 gm dextrose preceded by 50 mgs cortisone acetate orally 8 $^{1}/_{2}$ and 2 hours before the tests were performed. The SGTT was considered abnormal if the capillary blood glucose at 0.60 and 120 were greater than 120, 200 and 140 mg/100 ml (6.6, 11.1, 7.8 mmol/l) respectively. Capillary blood glucose considered abnormal for CGTT were 205 and 155 mg/100 ml at 60 and 120 (113 and 8.6 mmol/l) respectively. The SGTT was abnormal in 1 of the TAN patients and 2 controls while CGTT was abnormal in 9 TAN patients and 7 controls. However, all controls with abnormal CGTT were older than 50 years while only 1 TAN patient was older than 50 and 6 were 30 years or younger ($p = 0.0105$), Fischer's probability test. The results suggest a greater statistical risk for subjects with TAN 30 years or younger to have an abnormal CGTT. While this does not predict the future development of diabetes, our observation indicates the need for better designed prospective studies among such patients in developing countries.

Résumé

On a demontré que les patients souffrant de neuropathie ataxique tropicale (NAT) ont une intoxication chromique dûe au cyanure. Ont été analysés, il ya plusieurs années, les résultats d'un test de tolérance de glucose subi par un groupe de 88 patients souffrant de NAT et un autre groupe de 88 cas - témoins. Nous avons administré un test standard de tolérance de glucose (SGTT) avec 50 qm dextrose et un test de tolérance de glucose avec du cortisone (CGTT) avec 50 gm de dextrose; précédé de 50 mqs de cortisone acetate pris oralement 8[1]/2 et 2 heures avant le test. Le SGTT est considéré anormal si le glucose dans le sang capillaire a 0.60 et 120 etait plus haut que 120,200, et 140mq/100ml (soit 6.6, 11.1, 7.8mmol/l) respectivement. Le glucose du sang capillaire considéré anormal pour le CGTT était 205, et 155mq/100ml à 60 et 120 (11.3 et 8.6mmol/l) respectivement. Let SGTT était anormal chez un des patients souffrant de NAT chez 2 cas témoins tandis que CGTT était anormal chez 9 patients (avec NAT) et 7 cas témoins. Cependant tous les cas témoins avec CGTT anormal avaient plus de 50 ans tandis que seul un patient avec NAT avait plus de 50 ans et 6 avaient 30 ans ou moins ($p = 1.0105$) selon le test de probabilité de Fischer. Les résultats suggèrent une plus grande risque statistique chez les patients avec NAT âgés de 30 ans ou moins d'avoir un CGTT anormal. Bien que ces résultats ne constituent pas une prédiction du futur développement de diabète, nous observons que de meilleures études de tels patients s'avèrent nècessaires dans les pays en voie de développement.

Introduction

Tropical pancreatic diabetes (TPD) which was designated malnutrition related diabetes mellitus (MRDM) by the World Health Organization[1] is still a controversial subject. There is disagreement about proper nomenclature, classification, etiopathogenesis and doubt has been raised whether it is a distinct clinicopathological entity[2-5]. It is considered a heterogenous disorder and under the rubric are included the J (for Jamaica) type diabetes (protein deficient pancreatic diabetes — PDPD in the WHO classification), the Z (for Zudeima) type diabetes (fibrocalcific pancreatic diabetes — FCPD in WHO

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classification) and the K (for Kenya) type described by Mgola among patients in Nairobi, Kenya[8].

Important factors invoked in the pathogenesis of TPD are malnutrition[7,9-11] and cyanide intoxication from excessive consumption of cassava[9]. However, these associations were based largely on epidemiologic observations[9,10] and animal experimental studies[9-12,13]. In human subjects, there has not been any prospective long term study to confirm the association between malnutrition and TPD and no published data regarding the pathogenetic role of chronic cyanide intoxication in these patients.

A human model of chronic cyanide intoxication is the patient with tropical ataxic neuropathy (TAN). This syndrome was extensively studied by Osuntokun in Nigeria in the mid to late 1960s[14-16]. The disease comprises bilateral optic atrophy, sensorineural deafness and panmyelopathy with or without polyneuropathy[14-15]. Osuntokun showed conclusively that chronic cyanide intoxication of dietary origin was the most important factor in the etiology of TAN[14-16]. Nutritional education with elimination of excessive and exclusive cassava consumption led thereafter, to a complete eradication of the disease from areas of Nigeria where it was endemic. Consequently patients with TAN are not available presently, for a prospective evaluation.

During his extensive investigation of TAN, Osuntokun performed glucose tolerance tests on these patients and suitably matched controls[14]. In view of the interest in TPD and the questionable role of chronic cyanide ingestion in its pathogenesis, we have reviewed and analyzed the glucose tolerance test data in patients with TAN previously studied by Osuntokun as this will represent one of the first reports of such data in human subjects with proven chronic cyanide intoxication.

Materials and methods

This study was originally done by Osuntokun[14] in 1969.

Patients with TAN

The original patient population comprised 320 subjects who were studied over a 4 $^{1}/_{2}$ year period up to 1969. They were seen at the University College Hospital (UCH) Ibadan, or recruited during neurological surveys in villages of southwestern Nigeria. There were 165 males and 155 females and their ages ranged from 6 to 73 years.

Clinical diagnosis of TAN — This was based on the presence of at least two of the following: bilateral optic atrophy, bilateral sensorineural deafness, myelopathy of insidious onset, polyneuropathy.

Dietary history — This was noted to be poor in most of the patients. Cassava in various forms was consumed at least twice daily by many of the patients. Some of them also ate yam, maize, millet or beans and a few in the riverine areas also consumed fish.

Family and social history — All the patients belonged to low socio-economic class and in 41% of them, another family member was afflicted with TAN.

Stigmata of malnutrition — Painful glossitis, atrophy of filiform papilla, angular stomatitis, cheilosis, hair changes and non-hemorrhagic follicular hyperkeratosis were observed in 122 (38%).

Study cohort — Eighty eight among these 320 subjects with TAN were selected systematically for evaluation of their carbohydrate tolerance. Specific information about their sex and age distribution was not available but they had all the characteristics of the total population.

Controls — These comprised patients who were admitted into hospital for non-neurological diseases. Diabetes mellitus, renal or liver disease were excluded in all of them. Eighty eight of them, matched with the patients with TAN for age and sex had evaluation of their carbohydrate tolerance.

Glucose tolerance tests — Standard oral glucose tolerance test (S-GTT) and cortisone primed oral glucose tolerance test (C-GTT) were performed and interpreted as described by Jackson[17]. The S-GTT was done with 50 gm glucose load and blood sampling was every half hour for 2 $^{1}/_{2}$ hours. For the C-GTT, cortisone acetate was administered orally in a dose of 50 mg (or 62.5 mg if the subject weighed more than 160 lbs, 72.7 kgs) 8 $^{1}/_{2}$ and 2 hours before ingestion of glucose. Venous blood was collected in fluoride bottles and whole blood glucose was measured by the glucose oxidase method.

Interpretation of glucose tolerance tests

This was based on the method of Jackson[17]. For S-GTT capillary blood glucose values above 120 mg/dl (6.7 mmol/l) fasting, 200 mg/dl (11.1 mmol/l) at 1 hour and 140 mg/dl (7.8 mmol/l) at 2 hours were considered abnormal; the corresponding venous whole blood glucose values respectively are 100

mg/dl (5.5 mmol/l), 190 mg/dl (10.5 mmol/L) and 120 mg/dl (6.7 mmol/l). If all three values were exceeded, it was considered definitely diabetic; if only two, probably diabetic and if only one, the 2 hour values was exceeded, it was regarded as suspicious of diabetes. For C-GTT, capillary blood glucose values considered as upper limits of normal were 205 mg/dl (11.3 mmol/l) at 1 hour and 155 mg/dl (8.6 mmol/l) at 2 hours. Corresponding whole venous blood values were 185 mg/dl (10.3 mmol/l) and 135 mg/dl (7.5 mmol/l) respectively. In addition, at least one reading must be 50 mg/dl (2.8 mmol/l) or more above the corresponding reading during the S-GTT.

Methodologies for all other biochemical measurements are provided in the references[14,15].

Results

Nutritional status

The serum albumin, globulin and transferrin levels were similar in patients with TAN and controls. So also was their vitamin status as assessed by urinary excretion of thiamine, riboflavin, nicotinamide and folate. Table 1 demonstrates that the indices for cyanide intoxication were significantly higher in patients with TAN compared with controls. Though cigarette smokers had comparable thiocyanate (SCN) levels as patients with TAN, their plasma cyanide (CN) levels were significantly lower, $p < 0.0001$. The high SCN and CN levels in patients with TAN fell within 6 weeks of hospitalization with improved nutrition but increased to initial levels 12 weeks after hospital discharge.

*Table 1: A comparison of biochemical indices of cyanide intoxication in TAN** subjects and controls

Index	Category of subjects	N	Concentration (Mean ± SE)
Plasma thiocyanate (SCN) (umols/100 ml)	I. Patients with TAN	320	11.3 ± 0.24
	II. Controls-non-neurologic diseases	52	2.8 ± 0.2
	III. Controls-healthy hospital workers	49	2.0 ± 0.1
	IV. Controls-healthy smokers	18	8.3 ± 0.7
ANOVA :	F (3,407) = 101.1; p < 0.001+		
Plasma cyanide (CN) (umols/100ml)	Patients with TAN	108	0.999 ± 0.004
	Controls-non-neurologic diseases	106	0.027 ± 0.0017
	Controls-healthy smokers	18	0.058 ± 0.006
ANOVA :	F (2,229) = 53,511.5; p < 0.00001		
Urinary thiocyanate (SCN) umols/kg/24 hour	Patients with TAN	47	2.42 ± 0.12
	Controls-non-neurologic diseases	40	0.62 ± 0.005
t-test	p < 0.01		
Serum Vit. B12 (pg/ml)	Patients with TAN	320	1746 ± 76
	Controls-non-neurologic diseases	114	1430 ± 94
t-test	p < 0.05		

* Data Source (ref. 14)

** TAN — Tropical ataxic neuropathy.

ANOVA — Analysis of variance.

\+ Using t-test for pair-wise comparisons with Bonferoni's adjustment, no significant difference at 5% level between groups I and IV and between II and III.

Table 2: Glucose data in TAN* patients with abnormal cortisone glucose tolerance test

	Sex	Age	Test	Glucose data (mg/100 ml) + 0	30'	60'	90'	120'	150'
1.	F	19	S-GTT	53	98	131	142	92	49
			C-GTT	174	225	202	180	170	140
2.	F	17	S-GTT	86	114	138	108	97	92
			C-GTT	65	94	124	245	205	170
3.	M	58	S-GTT	93	97	165	79	52	68
			C-GTT	129	191	211	336	160	150
4.	F	20	S-GTT	77	103	117	102	74	70
			C-GTT	128	162	182	211	172	160
5.	F	30	S-GTT	71	103	109	100	81	75
			C-GTT	67	133	167	158	148	140
6.	M	35	S-GTT	70	75	79	108	81	70
			C-GTT	111	128	133	178	158	148
7.	M	19	S-GTT	71	113	124	103	81	70
			C-GTT	95	168	176	165	154	144
8.	M	25	S-GTT	58	93	116	84	76	66
			C-GTT	107	151	219	171	150	154
9.	F	39	S-GTT	93	113	106	113	106	95
			C-GTT	118	157	175	160	150	145

* TAN — Tropical ataxic neuropathy
+ Venous whole blood; to convert to mmol/l, divide by 18
S-GTT — Standard glucose tolerance test
C-GTT — Cortisone glucose tolerance test

Table 3: Abnormality of cortisone glucose tolerance test in patients and controls related to 30 years of age

	Patients with TAN	Controls	Total
Age ≤ 30 years	6	0	6
Age > 20 years	3	7	10
Total	9	7	16

TAN = Tropical ataxic neuropathy
Fischer's probability test: p = 0.0105

Glucose tolerance test (GTT) data

The S-GTT was abnormal in 1 of the 88 patients with TAN and this was a 60 years old female. Among the controls, the S-GTT was abnormal in 2 females aged 58 and 62 years. By contrast, the C-GTT was considered to be impaired in 9 of the patients with TAN and 7 of the controls. Table 2 presents the C-GTT data in the 9 patients with TAN who had abnormal tests by the criteria applied. The 2 hour glucose value was abnormal in all of them and in addition they all had at least one value 50 mg/dl (2.8 mmol/l) or more, higher than a corresponding value in the S-GTT. However, only 3 of them had an

abnormal 1 hour value. Further analysis revealed that while all the control subjects who had impaired C-GTT were above 50 years of age, in the patients with TAN, except for a female aged 58 years, 8 of them were under the age of 40 years and 4 were 20 years or younger. Table 3 is a two by two presentation of the proportions of abnormal C-GTT in the study subjects with 30 years as the dividing age. Chi-square analysis with Fischer's exact probability test demonstrated that the difference in the proportions of patients with impaired C-GTT under the age of 30 years was highly significant, $p = 0.0105$.

Discussion

The etiopathogenesis of TPD remains uncertain and controversial. The implication of cassava consumption and cyanide intoxication was based largely on circumstantial evidence from epidemiologic association[9-10]. This has been contradicted by findings from others studies[18]. There are few animal studies to confirm a true association[9,12,13] and fewer human studies other than a recent report by Akanji *et al.* [19] on acute feeding experiments of cassava derived meals. Also Swai *et al.* [20] have just published glucose tolerance test results among Tanzanian villages known to have high consumption of cassava. No association with impaired glucose tolerance or diabetes was observed but they did not provide serum cyanide data for their controls and also did not target those with neurological disease associated with heavy cassava consumption. The availability of glucose tolerance test data in a group of patients with TAN and matched controls provided a unique opportunity to determine whether chronic cyanide intoxication may affect carbohydrate tolerance.

The S-GTT did not show any difference in frequency of abnormal results in the patients with TAN and the controls similar to the observations of Swai *et al.* [20]. The C-GTT data suggests that for individuals with TAN under the age of 30 years, there is an increased statistical risk of having an impairment in carbohydrate tolerance when compared with controls. This observation is important for a number of reasons. Firstly, all forms of tropical pancreatic diabetes usually occur under the age of 30 years. Furthermore, previous evaluation of C-GTT by several investigators had suggested that a positive or abnormal test occurred with greater frequency in people over the age of 40 to 45 years[21], as was the case among controls in this study. It is however not certain that cyanide intoxication from chronic cassava consumption is the factor responsible for our observation. Handler[12] reported many years ago that very small amount of cyanide in the diet can impair glucose tolerance in rats. More recently, it was observed by Akanji and Famuyiwa[22] that there was impairment of glucose tolerance in weaning rats fed the following diets — protein replete cassava, protein deficient cassava, protein deficient corn and cyanide-supplemented protein deficient corn. However, cyanide supplementation of cassava free but protein replete diet had no effect on glucose tolerance, suggesting that other conditions are necessary for cyanide to impair glucose tolerance in rats.

The findings related to C-GTT in this study, intriguing as they are, should be interpreted with caution. Firstly, the number of participants in the study was small particularly with regard to detecting any true differences between patients with TAN and controls during S-GTT. The actual community prevalence of diabetes in Nigeria has not been reliably established although it has been cited to range from 0.5-2% [23]. Secondly, the method for the glucose tolerance tests does not meet currently suggested guidelines[24]. Furthermore, there were no agreed or uniform criteria for the interpretation of the C-GTT at the time the study was done. Table 4 indicates the several criteria cited at the time[25-27], including that of Jackson[17] that was used for patients in this study. Finally, the positive predictive value of an abnormal C-GTT for future development of diabetes is doubtful. West[28] concluded that the C-GTT was unlikely to identify with any appreciable accuracy, the presence of genetic susceptibility to diabetes. Most current opinion on the subject will support this view.

Table 4: Criteria for performance and interpretation of cortisone primed glucose tolerance test

Study	Glucose load	Glucose values (mg/100 ml)* 0	30	60	90	120	Glucose estimation
Fajans & Conn (25)+							
S-GTT	50 gms			> 160	> 135	> 110	Venous whole blood
C-GTT	50 gms			> 160		> 140	
Goto *et al.* (26)+							
C-GTT		Peak value		> 200 (180)		> 140 (125)	Capillary blood
Jackson (17)+							
S-GTT	50 gms	120 (100)		> 200 (180)		> 140 (125)	Capillary blood
C-GTT	50 gms			> 205 (185)		> 155 (135)	
Aronoff *et al.* (27)+							
S-GTT	100 gms	Summation of 0 to 180' > 600					Plasma
C-GTT	50 gms					170 (150)	

S-GTT — Standard glucose tolerance test
C-GTT — Cortisone glucose tolerance test
* — To convert to mmol/l, divide by 18
\+ — Reference
( ) — Approximate venous whole blood value.

Against this background, we can conclude that C-GTT but not S-GTT was selectively abnormal in young human subjects with proven chronic cyanide intoxication as exemplified by TAN. However, it cannot be inferred that this intoxication was primarily responsible for the selective abnormality of C-GTT or that it will cause impairment of carbohydrate tolerance or lead to diabetes. Nevertheless, the study highlights the need for carefully designed animal experiments and prospective studies in chronic cyanide intoxication as exemplified by TAN. The serious economic decline in many developing countries of Africa especially with the attendant severe nutritional problems could make such studies possible. Investigators in developing countries need to be aware about this and to evaluate such patients using currently accepted criteria for the performance and interpretation of glucose tolerance test. Such efforts have already begun as shown by the report of Swai *et al.* [20], but subjects with clinical and/or biochemical evidence of cyanide intoxication should be targeted for investigation and long term follow up.

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