Biochemical studies in Tanzanian patients with ataxic tropical neuropathy

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SUMMARY Data on thiocyanate and vitamin B₁₂ concentrations in plasma from Tanzanian patients with ataxic tropical neuropathy are presented and support the hypothesis that, as in Nigeria, the condition may result from chronic exposure to cyanide or cyanogens from a diet including large amounts of cassava.

In a series of reports describing clinical, epidemiological, and biochemical studies from W. Nigeria (Monekosso and Wilson, 1966; Osuntokun, 1968; Osuntokun, Durowoju, McFarlane, and Wilson, 1968; Osuntokun, Monekosso, and Wilson, 1969), it has been suggested that the occurrence in that country of a diffuse neurological disease which includes optic atrophy and sensory ataxia is related to the chronic toxicity of cassava, the main food for large numbers of people living in tropical and subtropical regions.

Biochemical evidence favours the hypothesis that the neurological disease may be the result of chronic exposure either to free cyanide or to its natural precursors, and further evidence has been sought by studying similarly affected patients in Tanzania, where a similar syndrome has been described (Haddock, Ebrahim, and Kapur, 1962).

PATIENTS AND METHODS

The majority of patients were adults attending the outpatient department of Muhimbili Hospital, Dar Es Salaam, and were all seen by one of us (W.J.M.). The criteria used for diagnosis of ataxic neuropathy were the same as those used in the Nigerian studies mentioned above—that is, sensory ataxia with or without signs of pyramidal dysfunction in upper or lower limbs, and optic atrophy. It is acknowledged that, although these criteria may be imprecise and give no idea of the underlying pathological process, they coexist with sufficient frequency both in

Nigeria and in Tanzania to represent a distinct syndrome.

Control subjects were selected from patients suffering from other organic diseases (neurological and non-neurological) and from psychiatric disorders, and blood was obtained either as outpatients or within 48 hours of admission to hospital.

Plasma from heparinized samples of venous blood was separated within one hour of collection and stored at -20° C until sufficient samples had accumulated within two months to transfer them packed in crushed ice and water in a vacuum flask by air to London.

Thiocyanate was determined by the method of Aldridge (1945) in plasma deproteinized with 10% trichloroacetic acid.

Plasma vitamin B₁₂ was estimated with *Lactobacillus leichmannii* (Matthews, 1962) on divided samples. As in the study of Monekosso and Wilson (1966), one aliquot was assayed after extraction with buffer containing cyanide (total vitamin B₁₂) and the other after extraction without added cyanide.

RESULTS

Mean plasma thiocyanate concentrations in patients and controls are shown in Table 1. Levels in the patients with neurological diseases are significantly higher than in both groups of controls ($P < 0.001$) and are similar to the values found in the Nigerian studies. The levels in controls are also similar in both series.

Mean plasma vitamin B₁₂ levels are shown in Table 2. The differences in B₁₂ concentrations obtained both with (B₁₂+CN) and without (B₁₂-CN) added cyanide during extraction are higher at the 5% level of significance in the

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TABLE 1

MEAN PLASMA THIOCYANATE CONCENTRATIONS IN PATIENTS WITH ATAXIC NEUROPATHY, AND IN CONTROLS WITH MISCELLANEOUS DISEASES, AND WITH PSYCHIATRIC DISORDERS

Patients with:		
Ataxic neuropathy (n=8)	Miscellaneous diseases (n=9)	Psychiatric disorders (n=10)
9.3 ± 1.9	2.8 ± 0.82	1.5 ± 0.14

Mean in μ -mole/100 ml., with numbers of patients, and SEM

TABLE 2

MEAN PLASMA VITAMIN B₁₂ CONCENTRATIONS IN PATIENTS AND IN CONTROLS, WITH AND WITHOUT CYANIDE EXTRACTION (B₁₂ + CN, AND B₁₂ - CN RESPECTIVELY) AND B₁₂ - CN EXPRESSED AS PERCENTAGE OF B₁₂ + CN

	Patients with:		
	Ataxic neuropathy n=8	Miscellaneous diseases n=9	Psychiatric disorders n=10
B ₁₂ + CN	700 ± 118	407 ± 60	479 ± 30
B ₁₂ - CN	380 ± 64	227 ± 34.2	268 ± 42
(B ₁₂ - CN) (B ₁₂ + CN) %	58.3 ± 8.8	57.6 ± 5.8	56.7 ± 3.8

Means in pg/ml., with numbers of patients and SEM.

patients with neurological disease and the miscellaneous controls, but B₁₂ - CN expressed as a percentage of total B₁₂ (B₁₂ + CN) is the same in all groups.

DISCUSSION

Although ataxic tropical neuropathy, the degenerative neurological syndrome described in Nigerians and Tanzanians, is clinically similar in both countries, there is a dearth of post-mortem studies of the condition, and therefore conclusions about their identity must be tentative.

Nevertheless, the demonstration of high plasma thiocyanate concentrations in patients in both countries suggests that in both groups there is an excessive exposure to cyanide or cyanide precursors. Cassava is not yet as popular a food in Tanzania as in W. Africa but, in the absence of data for the prevalence of the disease in Tanzania, it is impossible to know at present whether or not the less extensive use of cassava is reflected in a lower frequency of the disease. The findings presented here support the hypothesis that there is a risk of developing a progressive neurological disease after chronic cyanide

exposure. It is known that the detoxification of cyanide to thiocyanate requires a substrate of mercaptopyruvate or thiosulphate, both of which are derived from sulphur-containing amino acids that tend to be lacking in many tropical diets, and therefore protein malnutrition may also be a contributory factor. If so, the efforts to extend the use of cassava by agricultural advisers in developing countries should be accompanied by measures to improve the quality of the diet, as well as by the cultivation of strains of cassava which produce much smaller amounts of linamarin than present popular varieties.

It has been suggested that extraction of vitamin B₁₂ from plasma with added cyanide varies according to the exogenous exposure of the donor to cyanide (Smith, 1961). Thus the proportion of vitamin B₁₂ obtained without the addition of cyanide to the extraction buffer (B₁₂ - CN) expressed as a percentage of vitamin B₁₂ formed by extracting plasma with cyanide-containing buffer (B₁₂ + CN) is higher in smokers than in non-smokers (Wilson and Matthews, 1966). In the present study the significance of the serum vitamin B₁₂ findings is not clear and the contrast with those of Monekosso and Wilson (1966). It is noteworthy, however, that in a separate Nigerian series (Osuntokun, 1969) and in a series of Europeans with Leber's disease in whom a defect in cyanide metabolism has been postulated (Wilson, Linnell, and Matthews, 1971) total serum vitamin B₁₂ concentrations were higher than in controls. Further study of this complex relationship is needed.

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