J. Neurol. Neurosurg. Psychiat., 1967, **30**, 7

Role of vitamin B_{12} deficiency in tropical 'nutritional' neuromyelopathy

K. N. JEEJEEBHOY, N. H. WADIA, AND H. G. DESAI

From Radiation Medicine Centre, Medical Division, Atomic Energy Establishment, Trombay, Tata Memorial Hospital, Parel, Bombay, and the Department of Neurology, J. J. Hospital, Bombay

The term 'nutritional' neuromyelopathy has been applied to a wide range of heterogenous neurological disorders occurring especially in the tropics. The clinical manifestations of this condition are spinal cord syndromes which may be purely motor, purely sensory, or mixed, associated with retrobulbar neuropathy and eighth nerve deafness (Cruikshank, 1962). The cause of nutritional neuromyelopathy is unknown. In a detailed study of 206 cases from Jamaica, no definite aetiology was found and vitamin B_{12} deficiency did not occur in these patients (Montgomery, Cruikshank, Robertson, and McMenemey, 1964). On the other hand, a study of intestinal biopsy specimens of apparently healthy subjects residing in the tropics showed that tropical sprue may occur in a latent or atypical form (Klipstein, 1964). Since it is known that malabsorption of vitamin B_{12} may persist in clinically asymptomatic patients with tropical sprue (Sheehy, Perez-Santiago, and Rubini, 1961), it is likely that such asymptomatic cases may develop vitamin B_{12} deficiency and present clinically as cases of neuropathy.

On this assumption, 12 consecutive patients who presented with neuromyelopathy of obscure origin were investigated with a view to detecting malabsorption of different substances, including vitamin B_{12}. In all these patients, gastrointestinal symptoms were mild or absent and in six patients vitamin B_{12} deficiency was shown to be the cause of neuromyelopathy and was probably the cause in another two. Of these eight patients, six had clinically unsuspected intestinal malabsorption which conformed to the pattern seen in tropical sprue.

MATERIALS AND METHODS

SERUM VITAMIN ESTIMATIONS Serum vitamin B_{12} was estimated by a microbiological method using *Euglena gracilis* (Ross, 1952). Serum folate was estimated by a microbiological method using *Lactobacillus casei* (Waters and Mollin, 1961).

GASTRIC AND INTESTINAL FUNCTION STUDIES AND BIOPSY D-xylose absorption was estimated by feeding 5 or 25 g. of d-xylose in a pint of water and estimating the amount excreted in a five-hour collection of urine passed after the dose. Faecal fat estimations were performed by a wet method (van de Kamer, Huinink, and Weyers, 1949)

TABLE I

CLINICAL FEATURES OF PATIENTS WITH NEUROMYELOPATHY

Case No.	Sex	Age (yr.)	Peripheral Neuropathy[1,2]		Myelopathy		Gastrointestinal Symptoms		Mental Function	Pallor of Optic Discs	Clinical Response to Vitamin B_{12}
			Upper Limbs	Lower Limbs	Posterior Column	Lateral Column	Past	Current			
1	M	25	−	±(doubtful)	++(C)	++(A)	+(B)	+(B)	−	+	+(C)
2	M	43	+	++(A)	++(B)	−	+(C)	+(C)	−	+	+(C)
3	M	60	−	++(C)	++(C)	−	−	−	−	−	+(B)
4	F	34	−	++(A)	++(B)	−	−	−	+	−	+(C)
5	M	45	+	+	++(B)	−	−	−	−	−	+(B)
6	M	18	−	++(A)	++(C)	++(A)	+(C)	−	+	+	+(C)
7	M	70	++(B)	++(B)	++(B)	−	+(C)	−	−	−	+(B)
8	F	60	−	++(A)	++(C)	++(A)	+(C)	−	−	−	+(B)
9	M	27	+	++(B)	++(C)	++(A)	−	−	−	−	−
10	M	56	−	±(doubtful)	++(C)	++(A)	−	−	−	−	−
11	F	30	−	+(A)	++(C)	−	−	−	−	−	−
12	F	44	−	+(B)	++(C)	++(A)	+	−	−	−	−

[1] + subjective changes only, ++subjective and objective changes; [2]impairment: A, mild, B, moderate, C, severe; improvement: A slight, B good, C excellent.

TABLE II

RESULTS OF INVESTIGATIONS IN PATIENTS WITH NEUROMYELOPATHY

Case No.	Hb (g.%)	Bone Marrow	Serum B_{12} (μμg./ml.)	L. Casei (mμg./ml.)	$^{58}CoB_{12}$ Absorption without Intrinsic Factor		$^{58}CoB_{12}$ Absorption with Intrinsic Factor		Folic Acid Absorption	
					Schilling's Test (% excreted)	Faecal Excretion Method (% absorbed)	Schilling's Test (% of excretion)	Faecal Excretion Method (% absorption)	Peak Serum Concentration after Oral Folic Acid (40 μg./kg. body weight)	Absorption of ^{3}H Folic Acid (% of dose absorbed)
1	7·5	Megoblastic	12·5	29	0	—	7·1	—	87	—
2	10·5	Normoblastic[2]	40+[1]	13·3	0	—	2·8	—	32	—
3	10·5	Megaloblastic	50	0·8	0	—	3	—	4·5	—
4	14·3	Megaloblastic	12·5	6·0	—	0	—	5·6	—	26
5	14·7	Normoblastic[2] occasional giant meta-myelocytes	235[2]	11·5	—	22	—	—	—	—
6	10·0	Megaloblastic[1]	295[2]	9	—	0	—	—		21·3
7	10·0	Megaloblastic[1]	12·5	3·3	—	0	—	0·6	—	64
8	8·4	Megaloblastic giant meta-myelocytes	38	6·0	—	0	—	60·8	—	39·5
9	10·5	Normoblastic	165[2]	11·0	—	28	—	—	—	96·2
10	16·0	Normoblastic	500	5·3	12·7	—	—	—	45·7	—
11	12	Normoblastic, macronormoblastic gr. I[1]	222·5	4·7	—	76	—	—	—	54
12	14	Normoblastic	80	3·6	—	41·7	—	—	—	73·5
Normal values			75–1000	5–25	>10	>30	>10	>30	>40	>50

[1]Before any treatment.
[2]After injection of vitamin B_{12}.

on 2 × 3 day collections of faeces of patients who were on a diet containing 100 g. fat. Folic acid absorption was estimated by the method of Chanarin, Anderson, and Mollin (1958). Vitamin B_{12} absorption was measured with the aid of ^{58}Co vitamin B_{12} using the urinary excretion method (Schilling, 1953) or the faecal excretion method (Ganatra, Sundaram, Desai, and Gaitonde, 1965). The test was repeated with intrinsic factor given as 100 ml. of normal human gastric juice in six patients.

Gastric and jejunal biopsies were performed with the Crosby capsule (Crosby and Kugler, 1957).

The augmented histamine test (Kay, 1953) was done on 11 patients.

RESULTS

CLINICAL FEATURES The results are given in Table I.

AGE Six of the 12 patients were below 50 years of age.

DIETETIC HISTORY All patients were vegetarians and detailed dietetic histories in six showed that the average protein intake was low and varied from 32 to 40 g. per day of which only 2·5 to 7·5 g. was of animal origin. Therefore, the intake of first-class protein was very poor. The calorie intake was also low and varied from 807 to 1,363 Kcals per day. Although these figures are low by international standards, they are no different from those for other Indian vegetarian patients without neuropathy.

NEUROLOGICAL FEATURES All patients presented with neurological symptoms. Symptoms related to the alimentary tract were not given spontaneously by any patient, but were elicited in two patients on questioning. Sensory ataxia of the lower limbs was the striking feature in all patients and one patient (case 7) also had ataxia of the upper limbs. The ataxia was severe in eight patients (cases 1, 3, 6, 8-12) and moderate in the remaining four. Correspondingly, there was marked or moderate impairment of vibration and postural sensibility. In contrast, peripheral neuropathy was only mild or moderate in all patients except one (case 3). Peripheral neuropathy was observed only in the lower limbs in eight patients (cases 1, 3, 4, 6, 8, 10-12) and was present in all four limbs in the remaining four. However, neuropathy in the upper limbs was confined to subjective symptoms only in three of the four cases (cases 2, 5, and 9) and objective signs were present in one patient (case 7). Lower motor neurone paralysis did not occur in any patient and paraesthesia, peripheral cutaneous sensory loss, absent or sluggish ankle jerks, and tender calves pointed to a purely sensory peripheral neuropathy. One patient (case 1) had blunting to touch and pain up to D-8 dermatome.

The pyramidal tracts were affected to a mild degree in six patients (case 1, 6, 8-10 and 12) but muscular weakness was mild or absent and difficulty in walking was essentially due to ataxia.

TABLE II (*continued*)

RESULTS OF INVESTIGATIONS IN PATIENTS WITH NEUROMYELOPATHY

Faecal Fat Excretion (g./day)	*D-xylose Excretion (g. in 5-hr. urine)*		*Jejunal Biopsy*		*Gastric Biopsy*	*Augmented Histamine Tests*		
			Dissecting Microscope Appearance	*Histological Appearance*		*HCl (mEq./hr.) pH*		
	25 g.	*5 g.*					*Before*	*After*
11	—	—	Leaves	Normal	Atrophic gastritis	0·32	5·8	8·2
8	—	—	Convoluted	Partial villous atrophy	Atrophic gastritis	0·28	5·5	5·2
12	1·4[2]	—	Leaves	Partial villous atrophy	Atrophic gastritis	0·42	5·5	5·5
5·2	3·1[2]	—	—	—	—	4·6	2·5	2·0
5·8	1·6[2]	—	Leaves	Partial villous atrophy	—	9·14	5·5	2·5
3·5	—	—	—	—	—	—	—	—
13·7	—	2·4	Leaves	Normal infiltration + +	Mild superficial gastritis	0·6	7·0	7·0
3·6	—	0·37	Convoluted	Partial villous atrophy	Atrophic gastritis	1·01	7·5	7·5
12·03	—	2·9	Leaves + + Convoluted +	Partial villous atrophy	—	11·39	2·5	2·0
4·24	—	2·1	—	—	—	27·3	2·0	2·0
5·6	—	2·4	Leaves	Normal	Superficial gastritis	8·4	4·0	2·0
7·4	—	2·3	Convoluted	Partial villous atrophy	Normal	17·8	3·0	2·0
<6	>4·4	>1·5						

Early optic atrophy was seen in three patients (cases 1, 2, and 6) but visual acuity was not remarkably diminished.

Two patients (cases 4 and 6) had definitely impaired mental function consisting of apathy, sluggish response to questions, a dulling of the intellect, drowsiness, and irritability. Memory was good in both patients but one of these two patients (case 4) was uncooperative.

INVESTIGATIONS The results of investigations are given in Table II. Marked anaemia was not a prominent feature, only two patients had haemoglobin levels of below 10 g.% (cases 1 and 8). In most patients, the haemoglobin varied from 10 to 16 g.%. However, three patients (cases 2, 5, and 6) had already received some injections of haematinics before the study. The bone marrow was megaloblastic or had isolated giant metamyelocytes in seven patients (cases 1, 3, 4, 5, 6, 7, and 8). In the remaining five patients, the marrow was normoblastic; however, one patient with a normoblastic marrow (case 2) had received injections of liver extract elsewhere.

SERUM VITAMIN B_{12} Serum vitamin B_{12} levels were very low in three patients (cases 1, 4, and 7), subnormal in a further three patients (cases 2, 3, and 8), and above 75 $\mu\mu$g./ml., which is the lowest normal level found in vegetarians (Jeejeebhoy, Desai, Noronha, and Antia, 1966), in six patients (cases 5, 6, 9-12).

The serum folate level was subnormal in three patients (cases 3, 7 and 12), normal in eight (cases 2, 4, 5, 6, 8, 9, 10, 11), and high in one (case 1).

AUGMENTED HISTAMINE TEST This test was done in 11 patients (cases 1-5, 7-12). There was achlorhydria in five patients (cases 1-3, 7 and 8) in whom histamine did not change the *p*H of the stomach contents. In the remaining six patients (cases 4, 5, 9-12), acid secretion was normal, and, on giving histamine, the *pH* of the stomach contents fell to 2.

GASTRIC BIOPSY The four patients with achlorhydria had atrophic gastritis (cases 1-3 and 8).

ABSORPTION TESTS Vitamin B_{12} absorption was markedly reduced in nine patients (cases 1 to 9); intrinsic factor improved absorption in two (cases 1 and 8) but did not improve vitamin B_{12} absorption in the remaining patients with achlorhydria. Absorption with intrinsic factor was only tested in one patient with normal gastric function (case 4), as it was presumed that in the presence of normal acid secretion, intrinsic factor secretion would also be normal (Whiteside, Mollin, Coghill, Wynn Williams, and Anderson, 1964).

Folic acid absorption was reduced in five patients (cases, 2, 3, 4, 6, and 8) of 11 patients studied.

D-xylose excretion was reduced in four (cases 3, 4, 5, and 8) patients of nine studied.

Faecal fat excretion exceeded 6 g./day in six patients (cases 1-3, 7, 9, and 12) of 11 studied.

Jejunal biopsy was normal in five patients (cases 1, 7-9, and 11) and showed partial villous atrophy in four patients (cases 2, 3, 5, and 12).

Barium meal examination was done in six patients (cases 1-3, 7-9). In one patient (case 1), the ileum was mildly dilated, and in the remaining five there was generalized dilatation of the jejunum and ileum with thickening of mucosal folds.

DISCUSSION

In the present series of 12 patients with tropical neuromyelopathy of obscure origin, investigations showed that eight (cases 1-8) had vitamin B_{12} deficiency associated with malabsorption of this vitamin. Malabsorption was clinically latent and gastrointestinal symptoms were not prominent in any patient. Furthermore, giving vitamin B_{12} injections resulted in a moderate to marked improvement in the symptoms of patients with deficiency (Table I). On the other hand, four patients (cases 9-12), clinically indistinguishable from the group mentioned above, were not deficient in vitamin B_{12} and did not respond to the administration of this vitamin. The clinical similarity of these two groups can be appreciated by comparing the case histories of a representative member of each group (Appendix I). This observation underlines the need for careful investigation of such patients to determine whether vitamin B_{12} deficiency is present.

NEUROLOGICAL CHANGES The dominant feature was ataxia associated in some patients with spastic paraparesis. Mental changes and optic atrophy were also seen but deafness was not encountered. Peripheral nerve lesions were confined to a mild or moderate sensory neuropathy only.

HAEMATOLOGICAL CHANGES Serum vitamin B_{12} was low in six patients and indicated vitamin B_{12} deficiency. However, two patients with normal vitamin B_{12} levels (cases 5 and 6) had received vitamin B_{12} before the present study and these normal levels may not be indicative of their status before treatment. Furthermore, the presence of a megaloblastic marrow before treatment in one of these patients (case 6) and giant metamyelocytes in the marrow of the other (case 5) pointed to possible deficiency of either vitamin B_{12} or folate earlier. Since serum folate levels were normal in these patients, it is most likely that they had vitamin B_{12} deficiency. The response of the neurological features to vitamin B_{12} in these eight patients was further evidence of deficiency of this vitamin.

In the remaining four patients (cases 9-12), there was no evidence of vitamin B_{12} deficiency and they did not respond to injections of vitamin B_{12}.

CAUSE OF VITAMIN B_{12} DEFICIENCY Malabsorption of vitamin B_{12} was present in all patients who had deficiency of this vitamin. In six patients, the absorption of vitamin B_{12} did not improve with intrinsic factor and in these patients malabsorption was due to intestinal disease. Such patients had other evidence of intestinal disease like malabsorption of fat, d-xylose, and folic acid, together with atrophy of intestinal villi and changes in the intestinal pattern seen on barium meal examination. The overall picture in such patients was similar to that seen in tropical sprue (Jeejeebhoy *et al.*, 1966). In two patients (cases 1 and 8), absorption of vitamin B_{12} improved with intrinsic factor; both patients had achlorhydria on an augmented histamine test and atrophic gastritis, features similar to those found in pernicious anaemia. However, both also had atypical features not seen in pernicious anaemia. In the first patient (case 1), the young age and the presence of steatorrhoea suggesting intestinal disease are against his condition being one of uncomplicated pernicious anaemia. The second patient (case 8) also had malabsorption of folic acid and d-xylose indicating intestinal disease. These atypical features make it likely that these patients may be cases of sprue with associated gastric atrophy which is commonly found in tropical sprue (Floch, Thomasson, Cox, and Sheehy, 1962) and it is known that absorption studies in sprue may simulate those seen in pernicious anaemia (Vaish, Kumar, and Baker, 1964). The fact that pernicious anaemia is a genetically transmitted condition principally confined to north Europeans is also against our patients having Addisonian pernicious anaemia.

In contrast, in the patients without vitamin B_{12} deficiency, with one exception (case 9), the absorption of this vitamin was normal. Even in the patient with absorption of vitamin B_{12}, the degree of malabsorption was mild compared to the patients with vitamin B_{12} deficiency. Likewise, other gastric and intestinal function tests were normal in the majority of patients without vitamin B_{12} deficiency and abnormalities were only of a minor degree.

ROLE OF VITAMIN B_{12} DEFICIENCY IN NEUROMYELOPATHY Vitamin B_{12} deficiency appears to be an important cause of obscure so-called 'nutritional myelopathy' in India. The deficiency is due to

malabsorption of this vitamin probably as a result of clinically latent sprue affecting intestinal and gastric function. In the majority of patients with neuromyelopathy due to vitamin B_{12} deficiency, there were changes in both the stomach and small intestine causing malabsorption of this vitamin. In contrast, in patients with neuromyelopathy not due to vitamin B_{12} deficiency, gastric and intestinal functions were normal or only slightly altered. Furthermore, since the clinical features of patients with or without vitamin B_{12} deficiency are similar, such patients should be carefully investigated to determine the presence or absence of vitamin B_{12} deficiency. This is especially important as neuromyelopathy due to vitamin B_{12} deficiency showed excellent response to treatment.

SUMMARY

Twelve patients with tropical nutritional neuromyelopathy were investigated with a view to establishing the presence or absence of vitamin B_{12} deficiency in such patients and its cause. Eight patients were considered to have such deficiency and they improved with vitamin B_{12}. Four patients clinically indistinguishable from the other eight did not have vitamin B_{12} deficiency and did not improve with the administration of this vitamin.

The cause of vitamin B_{12} deficiency was due to intestinal malabsorption of this vitamin and although overt gastrointestinal symptoms were not observed in the majority of patients, absorption tests showed malabsorption of different substances, the pattern conforming to that found in tropical sprue.

Part of this work was carried out with the aid of the International Atomic Energy Agency Research Contract grant nos. 280/RB and 280/RI/RB.

APPENDIX I

REPRESENTATIVE CASE HISTORIES OF PATIENTS WITH (CASE 5) AND WITHOUT (CASE 10) VITAMIN B_{12} DEFICIENCY

CASE 5 A man, aged 45 years, was admitted with a history of tingling and numbness of all four limbs, ataxia, and a feeling of walking on cotton wool for about six months. The patient had a fall while climbing onto a bus about a month later and since then his symptoms worsened rapidly. He also observed weakness in both legs and hands for the last four months. The patient denied any gastrointestinal symptoms but had also lost about 10 lb. in weight in the last four months.

Examination revealed that, although he was well built and nourished, his nails were pale.

Central nervous system Higher functions, cranial nerves, fundi, and upper limbs were normal. There was incoordination of the lower limbs in the heel-knee test. He was ataxic on walking and the Romberg test was positive. There was no cutaneous sensory loss but vibration sense was impaired below the anterior superior iliac spines and postural sense at the toes. The deep reflexes were normal and the plantars were flexor.

Treatment and progress The patient had received injection vitamin B_{12} before admission. He was given injections of vitamin B_{12}, 200 μg. intramuscularly every three weeks, and he improved gradually in the next three months. The signs of posterior column involvement though distinctly improved were still persisting.

Conclusions Moderately severe sensory ataxia essentially due to posterior column involvement. Only subjective peripheral sensory nerve involvement in the form of paraesthesiae. Response to vitamin B_{12} was good but recovery was not complete.

CASE 10 A man, aged 56 years, was admitted with a history of ataxia and hesitancy of micturition for two years. The onset was gradual and the symptoms were gradually progressing. The patient had syphilis 25 years before and was treated with Salvarsan. He had no gastrointestinal symptoms in the past or at present.

On examination, the patient was well built and nourished (wt. 62.8 kg.); the nails were pink and tongue was normal.

Central nervous system The mental functions, cranial nerves, fundi and upper limbs were normal. Power and tone in lower limbs were normal. There was incoordination in lower limbs; vibration sense was absent below the anterior superior iliac spines and postural sense was also grossly impaired. Touch, pain, and temperature sensations were normal. There was no muscle tenderness. Romberg's sign was positive. Gait was wide based. The reflexes of upper limbs were normal. Both the knee jerks were exaggerated (Rt > Lt), and the ankle jerks were normal. Both the plantar reflexes were extensor.

The systemic examination was normal.

Treatment and progress He had received injections of vitamin B_{12} and prednisolone (outside the hospital) but had not shown any improvement. His symptoms and signs were the same when seen again after eight months.

Conclusions Posterior and lateral column involvement but no evidence of peripheral nerve involvement.

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