B12 deficiency — does it exist? —

a review by Justin van der Westhuizen

Introduction

Recent reports[1, 2] in the medical literature of neurological complications in cases of megaloblastic anaemia illustrate the importance of making an early diagnosis of vitamin B_{12} or folic acid deficiency. A group of workers at the Department of Neurology and Medicine at Tufts — New England Medical Center, Boston, describe the case of a 23-year-old woman with pernicious anaemia who demonstrated an unusually rapid and severe course of neurologic deterioration. She had taken folic acid intermittently for "mild anaemia" for one year before presentation. Diarrhoea developed, followed by malaise, weakness, myalgia, anorexia, confusion and drowsiness.

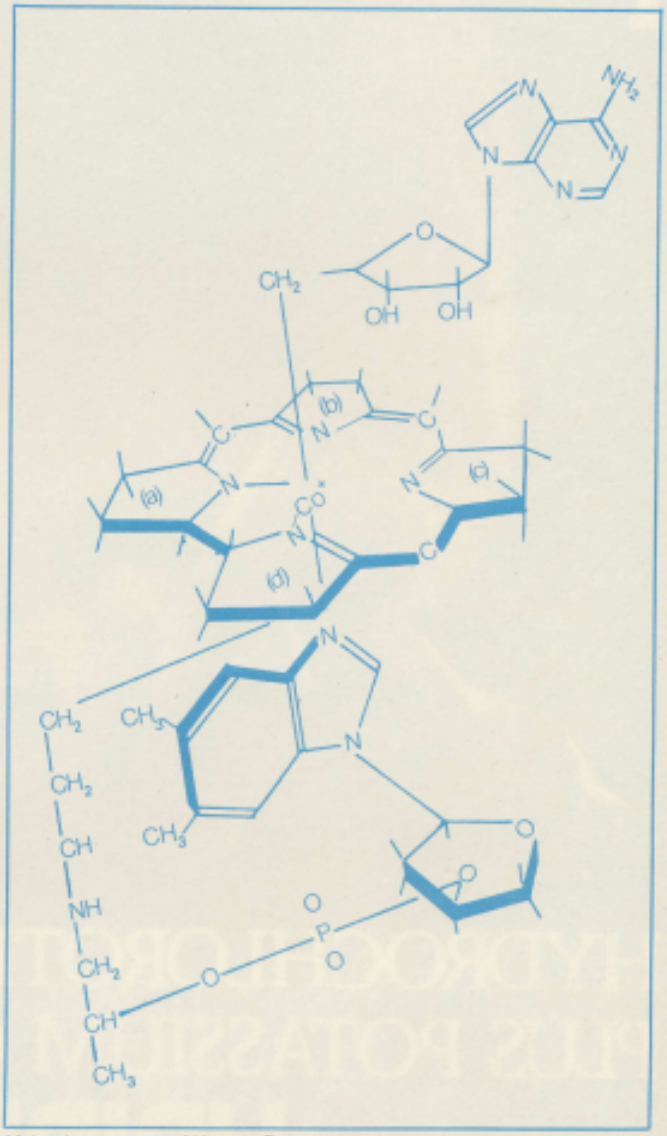
The muscle stretch reflexes and vibratory sensation at the ankles disappeared. A muscle biopsy specimen and X-ray of the gastrointestinal tract were normal. A diagnosis of hyperthyroidism was followed by treatment. However, a paranoid psychosis developed and a week later she became stuporous, with paralysis of all four limbs.

On examination she was pale and cachectic with a normal tongue. Posturing appeared normal and testable functions of the cranial nerves were intact. There was distal wasting of the limbs with arreflexia and absent plantar responses. Bone marrow biopsy showed megaloblastic erythropoiesis. Serum B_{12} level was 86 pg/mℓ (normal > 125 pg/mℓ) and serum folate was 12μg/L (normal 3 - 12 μg/L). Treatment was started with parenteral cyanocobalamin (1 mg. daily).

The patient's level of consciousness began to improve 12 days after commencing cyanocobalamin therapy. The reticulocyte reponse reached 17,8% on the 12th day, and the haemoglobin and MCV returned to normal levels after a month. After eight months, the severe EEG changes were reversed, strength returned to the arms, and while upper limb reflexes were normal, paraplegia remained with a T10 sensory level.

This case[1] emphasizes the danger of producing rapidly progressive neurological damage by folic acid in patients with pernicious anaemia. It also reminds one that vitamin B_{12} deficiency may be missed when the presentation is atypical, such as with malaise, weakness and confusion.

The remainder of this article will be devoted to a brief review of the neurological aspects of vitamin B_{12} deficiency.



Molecular structure of Vitamin B_{12}

Nutritional aspects

Vitamin B_{12} arises by bacterial synthesis and higher animals and man require the substance in their diet. The vitamin is absent from plants (fruit and vegetables) but present in the soil and all foods of animal origin, such as milk (3 ng/g), cheese (5 - 10 ng/g), eggs (7 - 30 ng/g), chicken liver (200 ng/g), fish (10 - 40 ng/g) and lamb (13 - 25 ng/g)[3]. The daily requirement of 2 - 5 μg daily is easily obtained from a non-vegetarian diet.

Causes of vitamin B_{12} neuropathy

The causes of vitamin B_{12} neuropathy are summarized in Table 1. Clearly the variety of factors which affect the absorption of the vitamin from the G.I.T. are aetiologically more important than dietary insufficiency.

Table 1.
Causes of vitamin B_{12} neuropathy

- Dietary Insufficiency (uncommon)
- Pernicious Anaemia
- Total or Partial Gastrectomy
- Chronic Alcoholism
- Gastric Carcinoma
- Intestinal Fistula or Obstruction
- Tropical Sprue
- Unclassified
- Pellagra

Cerebral manifestations

The cerebral manifestations have generally received less attention than the prominent spinal manifestations (subacute combined degeneration) although they occur in a significant percentage of cases. Cerebral symptoms may be mental and opthalmological, and include irritability, memory disturbances, mild depression, delusions, hallucinations, and coma[2, 4]. Since none of these symptoms are pathognomic, mental changes in B_{12} deficiency are difficult to distinguish from schizophrenic and other psychiatric disorders. The incidence of mental changes in various reports varies from about one-third to two-thirds of patients with pernicious anaemia[2, 4, 5].

The important pathological changes consist of a more or less diffuse, though uneven degeneration of the white matter with relatively little or no proliferation of microglia [6]. Microscopically the changes consist of foci of degeneration in the white matter involving myelin sheaths as well as axis cylinders. Adams and Kubic (1944) concluded that the cerebral lesions are essentially the same as subacute combined degeneration of the spinal cord [6]. A correlation between psychosis and neuropathologically demonstrable lesions in the brain with respect to severity has not been definitely established.

Optic atrophy

Visual disturbances in pernicious anaemia or subacute combined degeneration of the spinal cord have been recognised since the first descriptions of the disease during the last century. Several workers have found that visual disturbance can precede the other symptoms of pernicious anaemia. However, optic atrophy is a rare complication[3].

Subacute combined degeneration of the spinal cord

A neurological disorder in patients with pernicious anaemia was first described during the last century and termed "subacute combined degeneration of the spinal cord" by Russell and co-workers in 1900. Histologically the disease is characterised by demyelination, first in the dorsal columns and on the surface of the cord. These foci of demyelination spread up and down the cord. Although the early lesions are not confined to any particular tract, ultimately most of the dorsal columns, the pyramidal and spinocerebellar tracts become involved in the thoracic region.

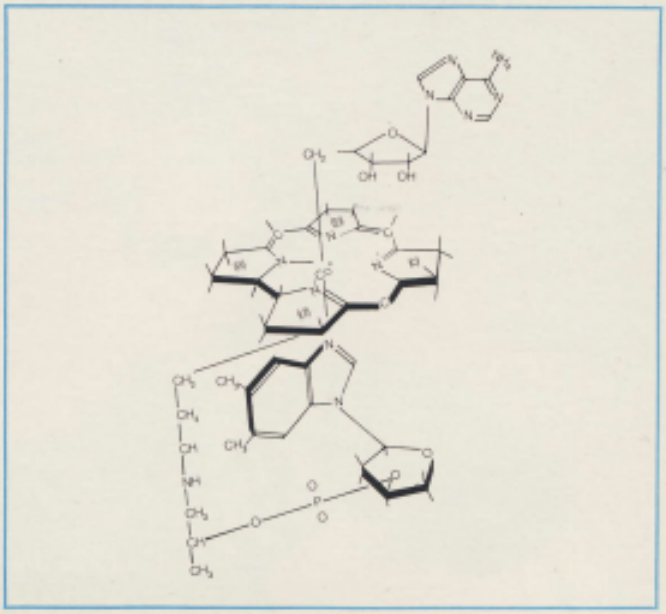
In the upper cervical segments, only the dorsal columns and spinocerebellar tract predominate. There is relatively little gliosis.

Three symptoms dominate the clinical picture, namely paraesthesia, disturbance in deep sensitivity and lateral column manifestations. The onset of symptoms[3] is usually insiduous with an average duration of 14 - 17 months. The common presenting symptoms are weakness, tiredness, dyspnoea, paraesthesiae and a sore tongue. With severe anaemia evidence of cardiac failure may appear, e.g. swelling of the feet. Loss of appetite and loss of taste are common and loss of weight is usual.

Dyspeptic symptoms are present in some and episodic diarrhoea in others. Vitamin B_{12} neuropathy usually presents with numbness, tingling, tightness or feelings of deadness or coldness in the limbs. The symptoms tend to progress from the lower limbs to the abdomen, and the arms may be affected later. Impotence in males can be an early symptom, and also difficulty with micturition.

Irritability, memory disturbance, and mild depression are common. Hallucinations which disappear following vitamin B_{12} therapy may occur. It should be noted that some patients have no symptoms at all, but are found because of macrocytosis on the blood count.

The symptoms and signs are summarised in Table 2, taken from the first comprehensive study[2] since the vitamin B_{12} assay became available in the 1950's. In addition, the neurological aspects of vitamin B_{12} deficiency were compared to that of folate deficiency. About one-third of each series had no abnormality, while about one quarter of each had evidence of organic mental change. There were some striking differences between the two deficiencies. Peripheral neuropathy was twice as common with vitamin B_{12} deficiency, while affective disorders (depression) were about twice as common with folate deficiency.



In the B_{12} deficient series, 61% had electrophysiological evidence of neuropathy (impaired conduction velocity or sensory action potential in sural or median nerves) compared to 21% in the folate series. Subacute combined degeneration was found in 16% of the vitamin B_{12} deficient patients, and not at all in the folate group. This study suggests that although there is a considerable overlap in the neurological complications of the two deficiencies, vitamin B_{12} deficiency has a greater effect on cord or peripheral nerve, whereas folate deficiency has a greater impact on mental function.

Table 2.

Incidence of neurological symptoms and signs (Shorvon et. al., 1980)[2]

	Vitamin B_{12} deficiency	Folate deficiency
Number of Patients	50	34
Mean Age (range)	60 (18-87)	40 (20-77)
Symptoms		
Weakness in legs	6%	3%
Ataxia	8	3
Paraesthesia: legs	18	6
Legs + arms	6	6
Signs		
Distal weakness	10	3
Ataxia	8	3
Absent ankle jerk	6	9
Arreflexia: legs	6	3
Legs + arms	2	3
Extensor plantars	16	-
Impaired vibration sense	40	6
Impaired joint position sense	10	3
Distal impairment of pain and temperature sense	2	3
Optic atrophy	2	-
Mental state		
Affective change	20	56
Organic change	26	27
No neuropsychiatric abnormality	32	35

Confirmation of the diagnosis

Because of the nonspecific nature of many of the symptoms, and the overlap between the neurological aspects of vitamin B_{12} and folate deficiency, reliance must be placed on special tests. The estimation of serum B_{12} and serum folate concentrations are essential, while the Schilling test for the absorption of B_{12} is a useful adjunct to diagnosis. In this test, an oral dose of radioactive vitamin B_{12} is given and the amount excreted in the urine determined.

When given orally, 0 - 3% is excreted by patients with pernicious anaemia, and 5 - 30% in normal subjects. If the excretion is in the low range, radiolabelled B_{12} is readministered together with intrinsic factor (which is required for the absorption of vitamin B_{12}). If the absorption improves, this provides evidence for intrinsic factor deficiency.

The diagnosis of megaloblastic anaemia is made by examining slides of the peripheral blood and bone marrow.

Biochemical mechanisms

The mechanism of the neural lesion in B_{12} deficiency is still unknown, while the haematological lesion is known to be due to a block in folate metabolism (methyl folate trap). Some workers[7, 8] have suggested that the odd and branched chain fatty acids that accumulate in the nervous system in B_{12} deficiency as a result of a block in the propionic acid metabolic pathway, may disturb myelin stability leading to demyelination.

The evidence for this is, however, not conclusive. Reynolds[9] has been suggesting for several years that a block in folate metabolism may underlie the neurological lesion, just as in the haematological lesion. A South African research group[10] has suggested that the neuropathy of B_{12} deficiency may be the direct result of the trapping and accumulation of methyl folate which is toxic in nervous tissue.

Evidence which supports this hypothesis inlcudes the observation that methyl folate (1) increases fit frequency in epileptics; (2) is present in synaptosomal fractions of the brain; (3) is readily transported into the nervous system; (4) resembles the neurotoxic compound kainic acid; and (5) when administered to B_{12} deficient patients increases the neuropathy. The central point of the hypothesis is that methyl folate, which accumulates in vitamin B_{12} deficiency becomes toxic at relatively high concentrations and leads to the neurological lesions.

This hypothesis may provide an answer for one of the major outstanding questions in this field.

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Justin van der Westhuyzen is Senior Research Assistant in the newly formed Brain Metabolism Research Unit of the South African Institute for Medical Research and the University of the Witwatersrand. He obtained his MSc from the same University in 1975, and is currently completing a PhD thesis on the neurological aspects of vitamin B_{12} deficiency in an animal model of the deficiency, the Egyptian fruit bat.

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