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Vitamin B12 Replacement Therapy and Its Rehabilitative Effects on Psychiatric and Neurologic Symptoms

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Introduction

Affecting over 5 million Americans and costing society over \$100 billion dollars annually, dementia has become a significant health problem (3,5,34). With the increasing geriatric population and the risk for becoming demented doubling every 5 years between 65 and 85 years of age (1% at age 65, 5% at age 75 and 15-25% at age 85) the idea of preventing or reversing dementia and other neurological disorders has stimulated numerous clinical investigations (1,2,5,14,19,21,22,24,33-36). The results of these investigations have led to the discovery of vitamin deficiencies causing myelopathy, peripheral neuropathy, optic atrophy, fatigue, insomnia, confusion, paranoia, depression and dementia (1-7,9-13,23,25,27,28, 32). Some authors believe that 30% of patients diagnosed with dementia have completely and/or partially reversible neuropathies (5,8, 11,12,16,17,19-22,24,28,33,36). The potential of reversal for any, and/or all of these neuropsychiatric symptoms has offered a ray of hope to the family members of those affected by any of these symptoms (19,27,32,34). Although vitamin B12 (cobalamin) deficiency has been associated with multiple neurological and psychiatric symptoms since the 1930's it has often been overlooked as a potentially treatable cause of dementia (TABLE 1) (4,6,7,10,18,21,26-31,34,35). Multiple clinical presentations, inappropriate screening methods, and lack of rigorous diagnostic criteria have all contributed to the misdiagnosis of cobalamin deficiency as a cause of reversible dementia (1-10,24,30,32-34).

Table 1: Psychiatric and Neurological Symptoms Associated with Vitamin B12 Deficiency

| Psychiatric Symptoms: | Definition |
|-----------------------|---|
| Dementia | Syndrome of acquired intellectual deterioration severe enough to interfere significantly with personal or social functioning. Cognitive impairments in orientation, recent memory, learning, attention, deficits in abstraction, judgment, comprehension, language and calculation. |
| Psychoses | Paranoia and Hallucinations |
| Delirium | Mental disturbance marked by illusions, hallucinations, physical restlessness, and incoherence. |
| Depression | Syndrome of dejected mood, psychomotor retardation, insomnia, associated with guilt feelings. |
| Epilepsy | Transient electrical disturbance of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, and sensory disturbance. |

| | |
|---|--|
| Bipolar disorder | Psychiatric disorder characterized by increased periods of activity or mania and depression |
| Attention Deficit Disorder | Inability to concentrate for prolonged periods of time |
| Neurologic Symptoms: | Definition |
| Peripheral Neuropathy | Bilateral symmetrical impairment of cutaneous sensation distally in the limbs, and/or absent and/or diminished tendon reflexes, with or without distal symmetrical atrophic limb weakness |
| Myelopathy | Spasticity, extensor plantar responses, or pathologic hyperreflexia with or without bilateral limb weakness; or a segmental vibratory or cutaneous sensory level |
| Myelopathy and/or neuropathy | Impaired proprioception, non-segmental diminished vibratory sensation, or autonomic symptoms such as postural hypotension, urinary, or rectal incontinence or impotence |
| Altered mental status | Impairment of attention span, memory, abstraction, fund of knowledge or other intellectual function with or without abnormalities of behavior, mood affect or logical thought |
| Optic neuropathy | Bilateral central visual impairment with or without optic atrophy |
| Paresthesias without abnormal neurologic findings | Spontaneous prickling, tingling, burning, numbness or related sensory complaints perceived predominantly in the feet or hands and feet without abnormal findings on neurologic examination |

Cobalamin is an essential vitamin for hematopoiesis and the maintenance of neurologic and psychiatric health (12,18, 22). Because it is not synthesized in the body, animals must obtain vitamin b12 from their diet (12,18, 22). Causes of cobalamin deficiency include: 1) inadequate dietary intake, 2) malabsorption due to inadequate levels of or a lack of secretion of intrinsic factor (causing pernicious anemia) 3) partial or total gastrectomy, 4) exposure to nitrous oxide (which oxidizes the cobalt atom impairing cobalamins' ability to function as a cofactor in the methionine synthetase reaction), 5) chronic renal failure 6) prescription drugs inhibiting vitamin B12 absorption, 7) increased requirement of vitamin b12, 8) increased cobalamin excretion, 9) increased cobalamin destruction by antioxidants (TABLE 2) (7,12,18,22). Because vitamin b12 is stored in the liver it can take 3-6 years before dietary vitamin b12 deficiency becomes clinically evident (12,18, 19,22). Although most often associated with pernicious anemia or megaloblastic anemia,

vitamin b12 deficiency can occur in the presence of normal hematological indices (7,12,18,19).

TABLE 2: CAUSES OF VITAMIN B12 DEFICIENCY

I. Inadequate dietary intake

- A. Poor diet (insufficient intake of meat and dairy products; adults need 1-2 mg/day)
 - 1. Vegetarian diet (lacking in meat, fowl, seafood, eggs, or dairy products)
 - 2. Chronic Alcoholism

II. Malabsorption

- A. Gastric Disorder (producing inadequate levels of or failing to secrete intrinsic factor)
 - 1. Pernicious Anemia (caused by vitamin b12 deficiency due to intrinsic factor secretion)
 - 2. Gastric mucosal atrophy (gradually progressing with age)
 - 3. Endocrine disorders (Hypothyroidism, polyendocrinopathy) associated with gastric damage

B. Gastrectomy

- 1. Gastrectomy (results in the loss of gastric parietal cells as the source of intrinsic factor)
- 2. Partial Gastrectomy (insufficient intrinsic factor secretion due to decreased number of gastric parietal cells)
- 3. Antibodies to intrinsic factor
- 4. Stress (implicated in reduction the amount of blood flow to the stomach, inhibiting vitamin b12 absorption)
- 5. Drugs inhibiting Vitamin B12 absorption
 - a. Colchicine
 - b. Neomycin
- 6. Decreased hydrochloric acid production (alkaline pH)

IV. Increased requirement (adult requirement is 2-4 ug/day)

- A. Hyperthyroidism
- B. Increased Hematopoiesis
- C. Infancy

V. Increased Excretion

- A. Inadequate vitamin B12 binding protein in serum
- B. Liver disease (inadequate storage capacity for vitamin B12)
- C. Renal disease

VI. Increased destruction by Antioxidants

- A. Pharmacological doses of vitamin C

Vitamin B12 is quintessential for the conversion of methylmalonyl-coA to succinyl-coA (Fig. 1) and in the synthesis of methionine (Fig. 2) (1,2,12,13,18,19). Contingent upon

adequate vitamin b12 levels the de novo synthesis of methionine involves the transfer of a methyl group from n-methyltetrahydrofolate to homocysteine, with the associated formation of free tetrahydrofolate (1,2,7,8,12-14,18,19). A deficiency in vitamin b12 impairs this reaction causing 1) the decreased synthesis of S-adenosylmethionine (SAM), 2) lack of free tetrahydrofolate, 3) accumulation of homocysteine levels (t-Hcy), and 4) accumulation of methylmalonic acid (MMA) (1,2,8,12-14,18,19). SAM is the essential methyl donor for a number of methylation reactions, while tetrahydrofolate is a necessary precursor of pyrimidine and purine synthesis. Therefore, a deficiency in vitamin b12 leads to deficient DNA synthesis and the hematological manifestation of megaloblastosis (1,2,6,7,34-36). Wilson observed in the 1930's that mental lassitude, confusion and memory loss could occur several years before the appearance of anemia. Despite Wilson's astute observation, up to 30% of patients with cobalamin deficiency have been misdiagnosed (7,35).

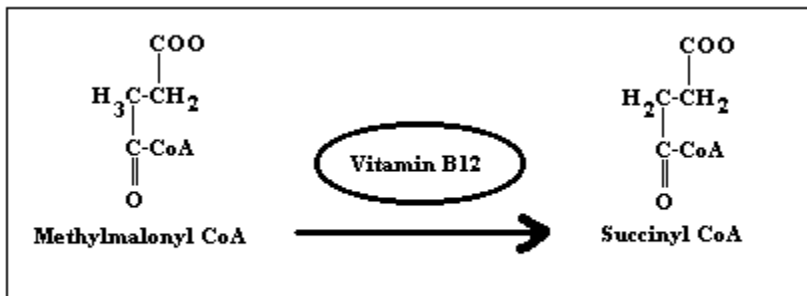


Fig 1: Reaction requiring Vitamin B12

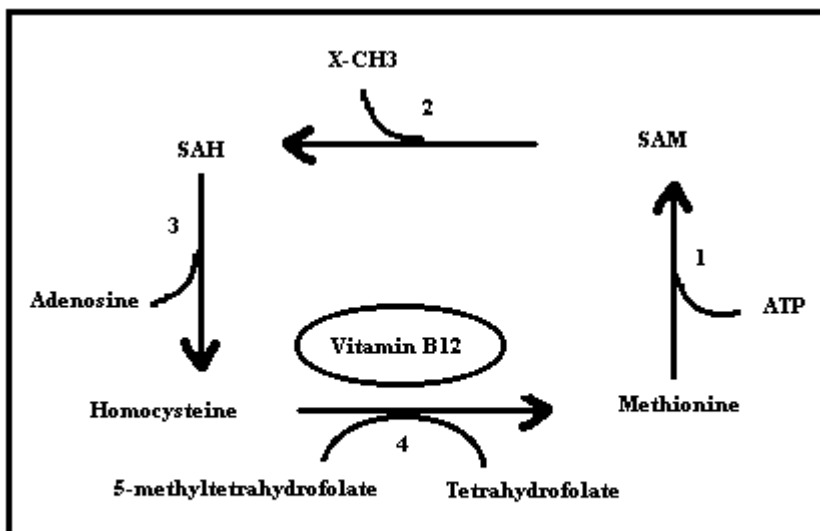


Fig. 2. Methylation reaction central to the biochemical basis of neuropsychiatric disorders of vitamin B12 deficiency. Key enzymes: 1. methionine adenosyltransferase; 2. x-methyltransferase; 3. S-adenosylhomocysteine hydrolase; 4. methionine synthase.

A second obstacle to the identification of vitamin b12 deficiency associated with dementia has been the belief that the Schilling test, the most commonly used biochemical

test for the diagnosis of cobalamin deficiency, can determine low serum vitamin b12 levels (7,18). Several researchers have found that the results of the Schilling test may be misleading because some patients with abnormally low serum vitamin b12 levels may be able to absorb radioactive vitamin b12 but cannot degrade vitamin b12 bound to food (7, 18). Another problem with the Schilling test comes from the interpretation of the "normal" results. Low results on the Schilling test, signifying normal cobalamin levels can be caused by: 1) incomplete urine collection, 2) renal disease, which impairs urinary excretion of radioactive vitamin b12, 3) malabsorption of cobalamin intrinsic factor due to small bowel disease, and 4) bacterial overgrowth in the intestines (7,12-14,18,29,32,34). Newer biochemical tests that measure MMA and t-Hcy levels have been more effective in the early and accurate diagnosis of patients with cobalamin deficiency (8,18). Although more accurate MMA and t-Hcy tests are expensive and require the use of sophisticated equipment (8,18). Measurements of cerebral spinal fluid (CSF) vitamin b12 levels, in spite of the fact that it is an invasive procedure, has proven to be extremely effective at diagnosing cobalamin deficiencies (6,7,12-14,18,29,32,34,36).

A third obstacle in the identification of cobalamin induced neuropathy is the belief serum vitamin b12 levels indicate when replacement therapy should be initiated (6,7,18). Indeed, patients with low normal cobalamin levels (150 pmol/l) have increased levels of MMA and t-Hcy characteristic of tissue cobalamin deficiency (6,7,12,18). One study found that relying on serum vitamin levels alone underestimated the prevalence of increased levels of metabolites by as much as 50% (12). Some studies have discovered that neuropathy and myelopathy can occur at levels up to 300 pmol/l, normal reference range in the US is 200-400 pmol/l (6,7,18). These studies suggest that individuals may differ in the metabolic requirements of vitamin b12 (12,18). A recent study has suggested that current reference ranges may not be equally applicable to individuals of different races; lower limits for blacks and caucasians differing by as much as 40% (18). Therefore, setting a cut-off value as to when vitamin b12 replacement therapy should be initiated may lead to a failure of detecting a reversible dementia which has a 75% chance of being reversed when detected early enough (6,7,12,18).

What is the mechanism by which Vitamin B12 deficiency is associated with dementia?

In the absence of vitamin b12, homocysteine levels increase, since it is both a product of the SAM methylation reaction and precursor for the de novo synthesis of methionine (1,2,8,12,18). In fact greater than 95% of cobalamin deficient patients have been found to have elevated homocysteine levels (1,2,8,12,18,34). High homocysteine levels may produce toxic effects by shifting the equilibrium toward S-adenosylhomocysteine (SAH) (8,18,34). SAH competes with the remaining SAM for active site on the methyltransferase enzyme, essentially inhibiting monoamine neurotransmitter metabolism, protein and phospholipid methylation (1,2,18,34). High homocysteine levels have also been implicated in excitotoxicity through the activation of NMDA receptors (1,2). Activation of NMDA receptors is essential for the process of memory formation called long term potentiation (15). Homocysteic acid, a product of homocysteine oxidation, has been shown to be a potent NMDA channel agonist. The massive activation of the NMDA channel causes increased intracellular calcium levels, activation of calcium

dependent proteases and formation of toxic free radicals (15). It is the neurotoxic effects of NMDA receptor activation that are believed to be the cause of memory loss and dementia associated with vitamin B12 deficiency (1,2,34-36).

What is the evidence for cobalamin responsive neuropsychiatric abnormalities?

Although a relationship between cobalamin deficiency and neuropsychiatric disorders has been known to exist since the 1940's the specific cognitive effects of cobalamin replacement therapy have yet to be resolved (19,35). Despite some controversy over the effectiveness of cobalamin therapy, there is growing evidence that subjects with low serum cobalamin levels suffering from dementia, displayed significant cognitive improvement and/or resolution of their cognitive defects after prolonged cobalamin therapy (18,19). A study on geriatric patients suffering from dementia having serum cobalamin levels of less than 150 pmol/L revealed that there was a striking correlation between the duration of cognitive symptoms and the patient's response to therapy. Martin found that patients who suffered from dementia for less than twelve months experienced the greatest improvement in memory, construction, initiation and conceptualization after six months of cobalamin therapy, while patients who were symptomatic for greater than twelve months had little, if any, improvement. He further established the idea that there may be a therapeutic window for which cobalamin therapy is effective at ameliorating and/ or completely reversing the neuropsychiatric symptoms associated with low serum cobalamin levels (6,19). Neuronal plasticity, the ability of damaged neurons to repair themselves, may account for Martin's finding that there is a therapeutic window for which cobalamin therapy is effective. The longer the duration of symptoms, the less able neurons are able to replace lost connections, and the less effective is any type of therapy (6,19).

Numerous studies have found that the effects of vitamin b12 deficiency are not always reversible, especially if they have been going on for a prolonged period of time (6,19). Unfortunately, this was the case for a 45 year old man who was not diagnosed as being cobalamin deficient until 12 years after his initial symptoms. At the time of diagnosis the patient had marked peripheral neuropathy, paresthesia, impaired vibratory sense, loss of joint position sense and incontinence. After diagnosis and treatment the patient showed improvement in his cognitive functions, and was able to stand and walk with a walker but remained incontinent despite continued therapy (25). A study of six vitamin b12 deficient infants with marked developmental regression and poor brain growth had significant improvement with oral vitamin b12 supplements but psychometric testing at 5 years of age revealed that 2 patients were mildly retarded while the remainder functioned at or below normal levels (9).

The lack of conclusive evidence on the benefits of cobalamin can be attributed to inadequate biochemical tests. The use of neuropsychiatric tests which may not adequately measure mental status or be sensitive enough to measure changes over time, have contributed to the discrepancy over deficiency levels and therapeutic doses. Furthermore, some studies may not have been able to detect any cognitive improvement following

cobalamin therapy because they failed to allow sufficient time to elapse after the initiation of therapy for recovery to occur.

Vitamin b12 deficiency has also been overlooked as a potential cause of dementia because it has the same clinical presentation as Alzheimer's disease (6,20). Such observation coupled with the biochemical findings that patients with Alzheimer's associated dementia and patients with cobalamin deficiency have identical neuropsychiatric symptoms, low serum and low CSF vitamin b12 levels make a differential diagnosis virtually impossible (6,18,20). Recent studies have revealed that vitamin B12 CSF levels are markedly reduced in patients' with Alzheimer's compared to patients suffering from cobalamin induced dementia suggesting a method of differentiating between these two disorders (2,6,19,20,34). In light of the evidence that a significant portion of Alzheimer's patients have low serum and/or low CSF cobalamin levels ruling out co-existing disorders is critical in determining who responds to treatment for cobalamin responsive neuropsychiatric abnormalities (2,19,20).

Based on the evidence cited in this review, serum cobalamin screening should be performed on all patients over 65 years of age especially those patients with unexplained neuropsychiatric symptoms. If serum cobalamin levels are normal but dementia and neuropsychiatric symptoms due exist Yao suggests that serum methylmalonic acid and total homocysteine levels should be screened since patients with symptoms or signs of cobalamin deficiency who have responded to cobalamin therapy, can have normal cobalamin levels (6,12,18,19,36). The risk of failing to detect a true deficiency with a false negative screening prompts reconsideration of the threshold for treatment in patients with borderline cobalamin levels (12,36).

Potentially irreversible neuropsychiatric changes due to low cobalamin levels are avoidable (6,12,19,36). Early detection of low levels of cobalamin is imperative for treatment to be effective (6,12,19,36). Reports by Yao and Martin have suggested that treatment must be initiated within a one year from the onset of neuropsychiatric abnormalities for symptoms to be completely reversed (19,36). Moreover, treatment of the deficiency, however late may prevent the symptoms from getting worse (6,12,19,36). There are no known detrimental effects of vitamin b12 replacement therapy (12,18). The lack of detrimental effects of vitamin b12 replacement therapy, coupled with the potential of having improved psychiatric and neurological symptoms, should convince physicians that cobalamin therapy is worth pursuing.

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