

Vitamin B12 Could be A “Master Key” in the Regulation of Multiple Pathological Processes

Ilia Volkov, Yan Press and Inna Rudoy

Department of Family Medicine, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

Abstract

Multifunctional systems must maintain homeostasis. Man is an ideal example of a system that constantly aspires to attain optimal regulation, even under the stress of severe disease. We assume that there are universal, interchangeable (as required) biologically active substances that regulate the system and try to keep it in balance. We propose that one of these substances is vitamin B12.

Why vitamin B12? The list of organs and body systems in which vitamin B12 plays a functional role is constantly being added to. Vitamin B12 affects the normal growth of children, the peripheral and central nervous systems, bone marrow, skin, mucous membranes, bones, and vessels.

It is possible that even when the serum cobalamin level is normal, treatment with vitamin B12 could correct defects caused by other biologically active substances. We call this phenomenon the “Master Key” effect. We suggest that this “Master Key” concept can be tested by treating diseases, such as recurrent stomatitis, various forms of hyperpigmentation, trophic ulcers, and burns, with vitamin B12, even if the B12 serum level is normal.

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Key words: vitamin B12, cobalamin, vitamin B12 supplementation

Background

Multifunctional systems must maintain homeostasis. Man is an ideal example of a system that constantly aspires to attain optimal regulation, even under the stress of severe disease. We assume that there are universal, interchangeable (as required) biologically active substances that regulate the system and try to keep it in balance. We propose that one of these substances is vitamin B12.

Why vitamin B12? The importance of vitamin B12,

its multifunctional role, and its potential to play a role in the regulation of other biologically active substances are reflected in the extensive body reserves of vitamin B12 and the multiple system malfunctions that may occur in its deficiency. To date no case of B12 intoxication has been reported despite high-dose therapy.

We will attempt to demonstrate vitamin B12's critical roles by surveying and analyzing available reports, and on the basis of our own clinical experience.

Correspondence to Ilia Volkov, MD, Department of Family Medicine, Faculty of Health Sciences, Ben-Gurion University of the Negev, Lea Imenu St. 59/2 Beer-Sheva 84514, Israel

E-mail: r0019@zahav.net.il

Journal Website (<http://www.nms.ac.jp/jnms/>)

Vitamin B12 and Development

Neonates who are breast fed by mothers with vitamin B12 deficiency are already at risk for severe developmental disorders in their first days of life. The following cases, one in a human infant and one in a beagle, are representative of this development risk.

A 7-month-old boy presented with lethargy and failure to thrive. The boy's mother, who was a strict vegetarian, breast-fed him from birth. No other nutritional information was provided. Results of laboratory tests revealed macrocytic anemia and methylmalonic aciduria, consistent with vitamin B12 deficiency anemia. The infant responded well to vitamin B12 supplementation and was developmentally normal by 11 months of age¹.

A 6-month-old beagle presented with a 3-month history of failure to gain weight, lethargy, intermittent vomiting and seizures. Results of laboratory tests showed low serum cobalamin, anemia, leucopenia, and methylmalonic aciduria. Because the dog was receiving a balanced commercial canine diet, these results suggested congenital selective cobalamin malabsorption. Treatment with biweekly injections of cyanocobalamin at a dose of 50 mcg/kg corrected the cobalamin-deficient state and reversed all clinical abnormalities. Selective cobalamin malabsorption has previously been described in giant schnauzers and border collies and represents a unique, but readily treatable, hereditary metabolic disorder².

Present and Future Cobalamin-responsive Neuropsychological Conditions

The only function that is recognized as unique to vitamin B12 is the synthesis of myelin, a component of the sheaths that protect nerve fibers. Vitamin B12 deficiency can cause peripheral neuropathy and combined system diseases involving demyelination of the dorsal columns and the corticospinal tract. The following cases demonstrate these impairments.

Four patients presented with progressive sensory deficit, pyramidal tract symptoms, and postural

instability. Blood tests revealed megaloblastic anemia and vitamin B12 levels below the normal range. A magnetic resonance (MR) scan of the cervical spinal cord revealed subacute combined degeneration of the spinal cord, a neurological disease caused by vitamin B12 deficiency, in three of the four patients. This disorder can involve the posterior and lateral columns of the spinal cord, the peripheral nerves in some cases, the optic nerve, and the brain. Following parenteral supplementation with vitamin B12, the symptoms and the MR abnormalities either disappeared or improved significantly. Vitamin B12 deficiency can cause subacute combined degeneration of the spinal cord by interfering with myelin synthesis³.

A role for vitamin B12 has been suggested in the development, progression, and treatment of multiple sclerosis. Interferon (IFN)-beta is a mainstay therapy for demyelinating diseases but has only a partial effect on multiple sclerosis in humans and in several animal models of the disease. In a recent report the authors demonstrated a marked improvement in the clinical, histological, and laboratory findings of disease in *in vivo* mouse models of demyelinating disease. Such improvements were seen following combination therapy with IFN-beta and vitamin B12-cyanocobalamin (B12CN) in non-autoimmune primary demyelinating ND4 (DM20) transgenic mice and in acute and chronic experimental autoimmune encephalomyelitis in mice. Clinical improvement, manifested as near-normal motor function, was associated with reduced astrogliosis and demyelination. Combination therapy with IFN-beta and B12CN may be promising for the treatment of multiple sclerosis^{4,5}.

Complete or partial improvement, following vitamin B12 supplementation, has also been reported in memory loss⁶, depression⁷, psychosis⁸, and parkinsonism. The following case highlights an unusual presentation of vitamin B12 deficiency, i.e., acute-onset extrapyramidal syndrome.

A 55-year-old man presented with a 10-day history of decreased activity, including a slow gait, mild hand tremor, and almost inaudible speech. On physical examination, the patient had a mask-like face, reduced blink rate, and cogwheel rigidity. The

diagnostic work-up revealed vitamin B12 deficiency. Other causes for acute-onset parkinsonism were excluded by appropriate investigations. Treatment with intramuscular vitamin B12 injections led to a marked improvement in symptoms. At 5-year follow-up the patient was functionally independent with no neurological deficits⁹.

Common Hematological and Cutaneous Manifestations of Vitamin B12 Deficiency

Vitamin B12 affects bone marrow function. Vitamin B12 deficiency can result in megaloblastic anemia or pancytopenia. Vitamin B12 supplementation can also resolve generalized skin hyperpigmentation¹⁰⁻¹³. These features are illustrated in the following case.

A 16-month-old infant presented with neurological developmental regression, severe pancytopenia, excessive skin pigmentation, and tremor. The child had been breast-fed and refused to eat any other food. Laboratory studies showed severe pancytopenia, a reduced serum vitamin B12 level, and increased urinary methylmalonic acid. Results of bone marrow aspiration biopsy were compatible with megaloblastic changes. Results of a Schilling test were normal. The mother's serum vitamin B12 level was also low. Megaloblastic anemia resulting from inadequate vitamin B12 intake was diagnosed. Parenteral vitamin B12 therapy was started. The neurological deficit was not completely resolved, but the pancytopenia, tremor, and hyperpigmentation of the extremities resolved completely¹⁴.

Vitamin B12's Role in Decreasing Cardiovascular Events

There is little doubt about the association between vitamin B12 deficiency and homocysteinemia, or its role in the development of atherosclerosis. Numerous retrospective and prospective studies have revealed a consistent, independent relationship of mild hyperhomocysteinemia with cardiovascular disease and all-cause mortality. Starting at a plasma homocysteine concentration of approximately 10 $\mu\text{mol/l}$, the risk increases linearly with does without

a specific threshold level.

Hyperhomocysteinemia, as an independent risk factor for cardiovascular disease, is thought to be responsible for approximately 10% of the total risk. Elevated plasma homocysteine levels ($>12 \mu\text{mol/l}$, moderate hyperhomocysteinemia) are considered cytotoxic and are found in 5% to 10% of the general population and in up to 40% of patients with vascular disease. Various calculation models, suggest that a reduction of elevated plasma homocysteine concentrations may prevent up to 25% of cardiovascular events. Treatment of hyperhomocysteinemia is recommended for the apparently healthy general population^{15,16}.

Potential Uses of Vitamin B12

We investigated and reported a case of paradoxical disappearance of chronic erythema nodosum, which had persisted for more than 6 months in spite of prolonged treatment with non-steroidal anti-inflammatory drugs. When the patient complained of paresthesias, a blood test for vitamin B12 revealed a prominent vitamin B12 deficiency. Since treatment was started with intramuscular vitamin B12 injections, both the paresthesias and the erythema nodosum have resolved¹⁷.

The precise role of vitamin B12 deficiency in the pathogenesis of recurrent aphthous stomatitis (RAS) is speculative. Cell-mediated immunity is suppressed, and there are changes in the epithelium of the tongue and the buccal mucosa. These changes are analogous to those seen in the blood and bone marrow in cases of insufficient DNA synthesis. We administered intramuscular cobalamin injections to a patient with RAS who had vitamin B12 deficiency. There have been no recurrences of RAS over the last 18 months¹⁸. Furthermore, we have also used vitamin B12 to treat an immunocompromised patient with RAS and have observed no recurrences over a 6-month period.

It has also been shown that supplementation therapy with folate and vitamin B12 reduces the incidence of hip fractures in patients with hemiplegia following stroke¹⁹.

Conclusion

The important role played by vitamin B12 in bodily processes is becoming increasingly clear as its involvement in a broad range of organs and systems is recognized and documented. Vitamin B12 affects normal growth and development in children, the peripheral and central nervous systems, bone marrow, bones, skin, mucous membranes and vessels.

Is there a “normal” serum level of vitamin B12? When have we attained the “correct” level? There are no generally accepted guidelines for the definition, diagnosis, treatment, and follow-up of cobalamin deficiency. Total serum vitamin B12 may not reliably indicate vitamin B12 status. To increase specificity and sensitivity in the diagnosis of vitamin B12 deficiency, the concept of measuring homocystein , methylmalonic acid , and holotranscobalamin II,- a sub-fraction of vitamin B12, has aroused great interest. Holotranscobalamin II as a biologically active vitamin B12 fraction, promotes the specific uptake of vitamin B12 by all cells²⁰. However, diagnostic algorithms using vitamin B12, methylmalonic acid, and homocystein measurements reflect studies in some academic centers, and their negative predictive values have not been established, therefore, this problem remains controversial¹⁶. The probability of “functional” vitamin B12 deficiency decreases with increasing levels of vitamin B12.

How can we explain the disappearance of generalized hyperpigmentation, and erythema nodosum as a result of vitamin B12 treatment? Is vitamin B12 supplementation effective because the B12 level is corrected or for other reasons? It is conceivable that even if the serum level of cobalamin is within normal limits, treatment with vitamin B12 could correct defects caused by other biologically active substances.

We have called this potential benefit the “Master Key” effect. We propose that this potential be tested by treating diseases such as RAS , hyperpigmentation of any type, trophic ulcer, and burns with vitamin B12, even if its serum level is

normal.

Because vitamin B12 has no known significant toxic effects and has a low cost- effectiveness ratio, it should be assessed for the treatment of conditions for which it has not been tried before.

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