

**CAN SUPPLEMENTATION WITH FOLIC ACID AND VITAMINS PREVENT STROKE AND DEMENTIA?
YES, VITAMIN B 12 MAY BE THE KEY, BUT NECESSARY MEASUREMENTS INCLUDE METHYLMALONIC ACID
AND HOMOCYSTEIN**

A.C. Ludolph

Department of Neurology, University of Ulm, Ulm, Germany

Vitamin B12 (Cobalamin) Deficiency is one of the most frequent metabolic changes which result in a neuropsychiatric symptomatology. Prevalence is estimated with 1-2 % in the European population, but deficiency is much more frequent in the elderly (prevalence between 17-44 %), patients suffering from gastrointestinal disorders, alcoholism and vegetarians. Vitamin B12 is predominantly produced by microorganisms in animals.

It is still largely unknown, even by neurologists, that vitamin B12 deficiency does not only produce haematological and gastrointestinal symptoms and the well-known myelopathy and axonal neuropathy. Instead, the spectrum of manifestations of vitamin B12 deficiency includes also depression, cognitive disturbances and – more rarely – psychotic symptoms. However, the epidemiology of the prevalence and incidence of these manifestations is not known. The frequency of vitamin B12 deficiency in the elderly strongly suggests that the differential diagnosis of initial stages of cognitive impairment must include vitamin B12 deficiency. In our own studies in more severely demented patients we found in about 25 % the typical biochemical pattern of vitamin B12 deficiency and therefore it is likely that this contributed to the syndrome of dementia.

In blood, vitamin B12 binds to different transport proteins, transcobalamin I, II, and III. Only 6-30 % of total serum cobalamin binds to transcobalamin II (holotranscobalamin) which is the critical step responsible for the cellular uptake of the vitamin.

Biochemically, two metabolic steps are critically dependent from vitamin B12:

1. Oxidation of fatty acids by the enzyme methylmalonyl-CoA-mutase. This enzyme requires B12 as a cofactor; in a situation of cellular deficiency methylmalonic acid, a potentially neurotoxic metabolite inhibiting mitochondrial ATP generation, is built up.
2. Methylation of homocystein to methionin. This step is catalysed by methionin synthase which needs folate and methylcobalamin as cofactors. Therefore, increases of homocystein are observed in deficiency states caused by folate and B12. The secondary decrease of the methyl donator methionin leads to an inhibition of methyltransferases which results in hypomethylation of various proteins of the brain (including basic myelin protein).

In addition, vitamin B12 deficiency leads to an impairment of hematopoiesis by a reduction of the activity of ribonucleotide reductase type 2 since this enzyme requires deoxyadenosyl-cobalamin as a cofactor.

It can be easily concluded that the critical metabolic steps resulting from B12 deficiency underlie varying metabolic influences, are quiet independent from each other and therefore the clinical symptoms resulting from B12 deficiency might be quiet heterogenous.

Diagnosis of B12 deficiency is traditionally based on the measurement of B12 levels in plasma or serum. However, this measurement includes the total B12 (bound to transcobalamin I, II, and III). Therefore, this test does not predict a cellular B12 deficiency since this is entirely determined by B12 bound to transcobalamin (holotranscobalamin). Whether measurements of holotranscobalamin are superior to B12 measurements alone remains to be shown in practice; recently a test for holotranscobalamin was marketed but results for sensitivity and specificity are unknown. Therefore, the most reliable tests for a cellular B12 deficiency remain the measurement of methylmalonic acid and homocystein levels in blood. Since homocystein levels are also dependent from other metabolic factors (including B6 and folate deficiency) and are associated with technical challenges, the most reliable assay for the diagnosis of cellular B12 deficiency remains the measurement of methylmalonic acid levels. For practical purposes, it is important to know that levels may be false positive in patients with renal disease since it correlates linearly with creatinin levels.

I conclude that

1. populations at risk for vitamin B12 deficiency include the elderly, patients with gastrointestinal diseases, alcoholics and vegetarians
2. therefore the differential diagnosis of B12 deficiency is particularly important for patients with milder forms of cognitive impairment, but also prevalent in patients with moderate and severe dementias
3. The measurement of methylmalonic acid is (in combination with homocystein) the gold standard for the diagnosis of vitamin B12 deficiency. The measurement of B12 levels alone does not exclude the presence of the cellular B12 deficiency.
4. Also, normal haematological parameter does not exclude metabolic changes resulting from B12 deficiency which may result exclusively in severe neurological damage.

References:

- Elin RJ, Winter WE (2001) Methylmalonic acid. A test whose time has come? Arch Pathol Lab Med 125:824-827
- Klee GG (2000) Cobalamin and folate evaluation: measurement of methylmalonic acid and homocystein vs vitamin B12 and folate. Clin Chem 46:1277-1283.
- Thomas L (2000) Vitamin B12. In: Labor and Diagnose (Thomas L, Hrsg.).
- Obeid R, Herrmann W (2007) Holotranscobalamin in laboratory diagnosis of cobalamin deficiency compared to total cobalamin and methylmalonic acid. Clin Chem Lab Med 45(12):1746-50.
- Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A, McDowell I, Papaionnou A (2006) Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev 20;(3):CD004655.