The multi-faceted basis of vitamin B(12) (cobalamin) neurotrophism in adult central nervous system: Lessons learned from its deficiency.

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Glial cells, myelin and the interstitium are the structures of the mammalian central nervous system (CNS) mainly affected by vitamin B(12) (cobalamin, Cbl) deficiency. Most of the response to the damage caused by Cbl deficiency seems to come from astrocytes and microglia, and is manifested as an increase in the number of cells positive for glial fibrillary acidic protein, the presence of ultrastructural signs of activation, and changes in cytokine and growth factor production and secretion. Myelin damage particularly affects the lamellae, which are disorganized by edema, as is the interstitium. Surprisingly, rat Schwann cells (myelin-forming cells of the peripheral nervous system) are fully activated but the few oligodendrocytes (myelin-forming cells of the CNS) are scarcely activated. The presence of intramyelin and interstitial edema raises questions about the integrity of the blood-brain barrier and blood-cerebrospinal fluid (CSF) barrier. The results obtained in the CNS of Cbl-deficient rats indicate that cytokine and growth factor imbalance is a key point in the pathogenesis of Cbl-deficient neuropathy. In the rat, Cbl deficiency increases the spinal cord (SC) synthesis and CSF levels of myelinotoxic cytokines (tumor necrosis factor (TNF)-alpha and soluble (s) CD40:CD40 ligand dyad) and a myelinotoxic growth factor (nerve growth factor), but decreases SC synthesis and CSF levels of a myelinotrophic cytokine (interleukin-6) and a myelinotrophic growth factor (epidermal growth factor, EGF). The in vivo administration of IL-6 or EGF, or agents antagonizing the excess myelinotoxic agent, is as effective as Cbl in repairing or preventing Cbl-deficiency-induced CNS lesions. An imbalance in TNF-alpha and EGF levels has also been found in the CSF and serum of patients with severe Cbl deficiency.

PMID: 19394404 [PubMed - as supplied by publisher]
Periventricular white matter lucencies relate to low vitamin B12 levels in patients with small vessel stroke.


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BACKGROUND AND PURPOSE: Blood-brain barrier dysfunction may be an early phenomenon in the development of the small vessel disease, which underlies white matter lesions. Because vitamin B12 plays a role in maintaining the integrity of the blood-brain barrier, we studied serum vitamin B12 level in relation to such lesions. METHODS: In 124 patients with first lacunar stroke, we measured serum vitamin B12 level and rated the degree of white matter lesions on MRI. RESULTS: Mean vitamin B12 level was 202 pmol/L (SD, 68.9). Thirty-nine patients (31.5%) had a vitamin B12 level less than the lower reference value of 150 pmol/L. Lower vitamin B12 level was (statistically significant) associated with more severe periventricular white matter lesions (odds ratio/100 pmol/L decrease, 1.773; 95% CI, 1.001-3.003), but not with deep white matter lesions (odds ratio/100 pmol/L decrease, 1.441; 95% CI, 0.881-2.358; ordered multivariate regression analysis). CONCLUSIONS: More severe periventricular white matter lesions in lacunar stroke patients relate to lower vitamin B12 levels. A possible causal relationship should now be studied prospectively.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19286604 [PubMed - indexed for MEDLINE]
[Nutritional deficiency of vitamin B12 in infancy as a cause of encephalopathy]

[Article in Spanish]

Mahfoud A, Domínguez CL, Rodríguez D, Giamporcaro R.

Publication Types:

- Case Reports
- Letter

PMID: 19340788 [PubMed - indexed for MEDLINE]
Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children.

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BACKGROUND: Recent research has highlighted the influence of maternal factors on the health of the offspring. Intrauterine experiences may program metabolic, cardiovascular, and psychiatric disorders. We have shown that maternal vitamin B12 status affects adiposity and insulin resistance in the child. Vitamin B12 is important for brain development and function. OBJECTIVE: We investigated the relationship between maternal plasma vitamin B12 status during pregnancy and the child's cognitive function at 9 years of age. METHODS: We studied children born in the Pune Maternal Nutrition Study. Two groups of children were selected on the basis of maternal plasma vitamin B12 concentration at 28 weeks of gestation: group 1 (n = 49) included children of mothers with low plasma vitamin B12 (lowest decile, < 77 pM) and group 2 (n = 59) children of mothers with high plasma vitamin B12 (highest decile, > 224 pM). RESULTS: Children from group 1 performed more slowly than those from group 2 on the Color Trail A test (sustained attention, 182 vs. 159 seconds; p < .05) and the Digit Span Backward test (short-term memory, p < .05), after appropriate adjustment for confounders. There were no differences between group 1 and group 2 on other tests of cognitive function (intelligence, visual agnosia). CONCLUSIONS: Maternal vitamin B12 status in pregnancy influences cognitive function in offspring.

Publication Types:
- Research Support, Non-U.S. Gov't

PMID: 19227049 [PubMed - indexed for MEDLINE]
PMCID: PMC2656635
Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment.

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Using the Bayley test, the mental and psychomotor development in a cohort of 253 children were evaluated. Maternal dietary intake of vitamin B(12) and folate was assessed from a semiquantitative questionnaire administered during the first trimester of pregnancy. Maternal genotypes of MTHFR (677C>T and 1298A>C), were ascertained by PCR-RFLP. The 677T and 1298C variant alleles were present in 59% and 10% of participants, respectively. A dietary deficiency of vitamin B(12) was negatively associated with mental development (beta = -1.6; 95% CI = -2.8 to -0.3). In contrast, dietary intake of folate (< 400 mg/day) reduced the mental development index only among children of mothers who were carriers of the TT genotype (beta = -1.8; 95% CI = -3.6 to -0.04; P for interaction = 0.07). Vitamin B(12) and folate supplementation during pregnancy could have a favorable impact on the mental development of children during their first year of life, mainly in populations that are genetically susceptible.

Publication Types:
- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 19178787 [PubMed - indexed for MEDLINE]
Vitamin B-12 and cognition in the elderly.

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Vitamin B-12 deficiency is often associated with cognitive deficits. Here we review evidence that cognition in the elderly may also be adversely affected at concentrations of vitamin B-12 above the traditional cutoffs for deficiency. By using markers such as holotranscobalamin and methylmalonic acid, it has been found that cognition is associated with vitamin B-12 status across the normal range. Possible mediators of this relation include brain atrophy and white matter damage, both of which are associated with low vitamin B-12 status. Intervention trials have not been adequately designed to test whether these associations are causal. Pending the outcome of better trials, it is suggested that the elderly in particular should be encouraged to maintain a good, rather than just an adequate, vitamin B-12 status by dietary means.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 19116332 [PubMed - indexed for MEDLINE]

Vitamin B-12 and Brain Health
Plasma vitamin B12 status and cerebral white-matter lesions.

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BACKGROUND AND OBJECTIVE: Elevated homocysteine has been associated with a higher prevalence of cerebral white-matter lesions and infarcts, and worse cognitive performance. This raises the question whether factors involved in homocysteine metabolism, such as vitamin B(12), are also related to these outcomes. This study examined the association of several markers of vitamin B(12) status with cerebral white-matter lesions, infarcts and cognition.

METHODS: The study evaluated the association of plasma concentrations of vitamin B(12), methylmalonic acid, holotranscobalamin and transcobalamin saturation with cerebral white-matter lesions and infarcts at baseline and cognition at baseline and during follow-up among 1019 non-demented elderly participants of the population-based Rotterdam Scan Study. Analyses were adjusted for several potential confounders, including homocysteine and folate concentration.

RESULTS: Poorer vitamin B(12) status was significantly associated with greater severity of white-matter lesions, in particular periventricular white-matter lesions, in a concentration-related manner. Adjustment for common vascular risk factors (including blood pressure, smoking, diabetes and intima media thickness) did not alter the associations. Adjustment for homocysteine and folate modestly weakened the associations. No association was observed for any of the studied markers of vitamin B(12) status with presence of brain infarcts and baseline cognition or cognitive decline during follow-up.

CONCLUSIONS: These results indicate that vitamin B(12) status in the normal range is associated with severity of white-matter lesions, especially periventricular lesions. Given the absence of an association with cerebral infarcts, it is hypothesised that this association is explained by effects on myelin integrity in the brain rather than through vascular mechanisms.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18977824 [PubMed - indexed for MEDLINE]
Vitamin B12 status and rate of brain volume loss in community-dwelling elderly.


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OBJECTIVES: To investigate the relationship between markers of vitamin B(12) status and brain volume loss per year over a 5-year period in an elderly population. METHODS: A prospective study of 107 community-dwelling volunteers aged 61 to 87 years without cognitive impairment at enrollment. Volunteers were assessed yearly by clinical examination, MRI scans, and cognitive tests. Blood was collected at baseline for measurement of plasma vitamin B(12), transcobalamin (TC), holotranscobalamin (holoTC), methylmalonic acid (MMA), total homocysteine (tHcy), and serum folate. RESULTS: The decrease in brain volume was greater among those with lower vitamin B(12) and holoTC levels and higher plasma tHcy and MMA levels at baseline. Linear regression analysis showed that associations with vitamin B(12) and holoTC remained significant after adjustment for age, sex, creatinine, education, initial brain volume, cognitive test scores, systolic blood pressure, ApoE epsilon4 status, tHcy, and folate. Using the upper (for the vitamins) or lower tertile (for the metabolites) as reference in logistic regression analysis and adjusting for the above covariates, vitamin B(12) in the bottom tertile (<308 pmol/L) was associated with increased rate of brain volume loss (odds ratio 6.17, 95% CI 1.25-30.47). The association was similar for low levels of holoTC (<54 pmol/L) (odds ratio 5.99, 95% CI 1.21-29.81) and for low TC saturation. High levels of MMA or tHcy or low levels of folate were not associated with brain volume loss. CONCLUSION: Low vitamin B(12) status should be further investigated as a modifiable cause of brain atrophy and of likely subsequent cognitive impairment in the elderly.

PMID: 18779510 [PubMed - indexed for MEDLINE]
Effects of vitamin B12 and folate deficiency on brain development in children.

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Folate deficiency in the periconceptional period contributes to neural tube defects; deficits in vitamin B12 (cobalamin) have negative consequences on the developing brain during infancy; and deficits of both vitamins are associated with a greater risk of depression during adulthood. This review examines two mechanisms linking folate and vitamin B12 deficiency to abnormal behavior and development in infants: disruptions to myelination and inflammatory processes. Future investigations should focus on the relationship between the timing of deficient and marginal vitamin B12 status and outcomes such as infant growth, cognition, social development, and depressive symptoms, along with prevention of folate and vitamin B12 deficiency.

Publication Types:

- Review

PMID: 18709887 [PubMed - indexed for MEDLINE]
Effects of a B-vitamin-deficient diet on exploratory activity, motor coordination, and spatial learning in young adult Balb/c mice.


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Elevated homocysteine levels resulting from vitamin B deficiencies have been hypothesized to contribute to functional decline. To investigate the effects of elevated serum homocysteine on neurobehavioral performances, young adult Balb/c mice consumed a vitamin-B-deficient diet or a control diet under free-feeding and pair-fed conditions. The B-deficient diet decreased body weight and food intake but increased water ingestion. Relative to either control group, vitamin-B-deficient mice were more active in the open field and in enclosed arms of the elevated plus-maze. However, vitamin-B-deficient mice were not impaired on sensorimotor coordination and spatial learning tests, swimming to a visible platform even faster than either control group. The main effect of this diet restriction was hyperactivity with no change in anxiety, coordination, and memory. It remains to be determined whether severer deficits are demonstrable in older mice.

PMID: 18061153 [PubMed - indexed for MEDLINE]
Biomarkers of folate and vitamin B(12) status in cerebrospinal fluid.

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Folate and vitamin B(12) are essential cofactors for the methionine/homocysteine cycle in the brain. These vitamins mediate the remethylation of homocysteine (Hcy), which affects the production of the universal methyl donor, S-adenosylmethionine (SAM), in the brain among other organs. Additionally, increased plasma concentrations of total Hcy (tHcy) are associated with cerebrovascular disease and can compromise the blood-brain barrier. tHcy concentrations in the brain and cerebrospinal fluid become increased in several psychiatric and neurological disorders. Disturbances in the transmethylation pathway indicated by abnormal SAM, S-adenosylhomocysteine or their ratio have been reported in many neurodegenerative diseases, such as dementia, depression or Parkinson's disease. Cobalamin is essential for neuronal generation and its deficiency can cause degeneration of the nervous system. Available data emphasize that deficiency of folate and vitamin B(12) can lead to elevated concentrations of tHcy and disturbed methylation potential in the brain. Therefore, acquired or inherited disorders in these metabolic pathways are associated with brain abnormalities and severe neurological symptoms that are mostly irreversible, even after providing the missing cofactors. This review discusses the relationship between brain and blood levels of key vitamins and metabolites related to one carbon metabolism.

Publication Types:

- Review

PMID: 17892439 [PubMed - indexed for MEDLINE]
BACKGROUND: Symptoms of Vitamin B (12) deficiency in infancy include growth retardation, regression of psychomotor development, muscular hypotonia and brain atrophy. Besides an inappropriate vegetarian diet of the infants, a vegan diet or a pernicious anaemia of the mother may lead to an insufficient vitamin B (12) supply of the child. PATIENTS AND METHODS: We report here the neurological symptoms of 4 fully breast-fed infants from mothers on vegan diet or with pernicious anaemia. DISCUSSION AND CONCLUSION: Vitamin B (12) deficiency can easily be diagnosed by detection of methylmalonic acid when measuring the organic acids in urine. Vitamin B (12) deficiency should be avoided or diagnosed as early as possible since a supplementation of mother and child can prevent neurological symptoms of the baby. Furthermore, the neurological symptoms of the infant with manifest vitamin B (12) deficiency are (partially) reversible.

Publication Types:
- Case Reports
- English Abstract

PMID: 17729202 [PubMed - indexed for MEDLINE]
[Effects of folic acid, vitamin B(6) and vitamin B(12) on learning and memory function in cerebral ischemia rats]

[Article in Chinese]

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OBJECTIVE: To investigate the effects of folic acid, vitamin B(6) and B(12) on plasma homocysteine and on learning and memory functions in focal cerebral ischemia rats. METHODS: Sprague-Dawley rats were randomly divided into four groups. They were sham operation group (Sham OP), middle cerebral artery occlusion model group (MCAO), MCAO + folic acid group (MCAO + FA) and MCAO + compound vitamin (folate, vitamin B(6) and B(12)) group (MCAO + CV). Plasma homocysteine was measured before and after supplementation and after ischemia. RESULTS: The level of plasma homocysteine in MCAO + FA and MCAO + CV groups were significantly lower than those in Sham OP and MCAO groups after supplementation and ischemia (6.92 +/- 1.04 micromol/L and (5.49 +/- 1.00) micromol/L vs (9.33 +/- 1.11) micromol/L, (10.90 +/- 2.03 micromol/L), P < 0.05. While in MCAO + CV group was lower than that in MCAO + FA group (5.49 +/- 1.00) micromol/L vs (6.92 +/- 1.04) micromol/L, P < 0.05. The neurological deficit scores and shock times in Y-type maze of MCAO + FA and MCAO + CV groups were lower than those in MCAO group (1.75 +/- 0.46 and 1.38 +/- 0.52 vs 2.62 +/- 0.52; 123.50 +/- 39.77 and 86.25 +/- 21.39 vs 173.25 +/- 46.32, P < 0.05). The correct times of MCAO + CV group in Y-type maze was higher than that in MCAO group (3.75 +/- 0.42 vs 2.12 +/- 0.45, P < 0.05). CONCLUSION: Folic acid intake could not only reduce plasma homocysteine concentration but also promote the recovery of the learning and memory functions of rats with cerebral ischemia. The effects of folic acid combined with vitamin B(6) and vitamin B(12) on cerebral ischemia rats was better than that of single folate.

PMID: 17708876 [PubMed - indexed for MEDLINE]
Vitamin B12 deficiency as a potential cause of dementia.


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There is a patient case with dementia and brain MRI massive abnormalities, probably in the course of vitamin B12 deficiency.

Publication Types:

- Case Reports

PMID: 16146118 [PubMed - indexed for MEDLINE]
INTRODUCTION: A deficient supply of vitamin B12 can appear early during the first months of life, with haematological and neurological symptoms in the form of progressive encephalopathy. CASE REPORTS: We describe two patients with megaloblastic anaemia and halted somatic and cranial perimeter development, accompanied by neurological involvement. Both of them had an increased rate of excretion of methylmalonic acid, as well as homocysteine, in urine with extremely low serum levels of vitamin B12, as compared to normal values. Both patients were breastfed only. The study of the mothers revealed asymptomatic pernicious anaemia. Treatment with hydroxycobalamine led to clinical recovery and psychomotor development progressively returned to normal. CONCLUSIONS: Vitamin B12 deficiency due to a shortage of supply from the mother must be taken into account in the differential diagnosis of possibly reversible severe encephalopathies.

Publication Types:
- Case Reports
- English Abstract

PMID: 15926134 [PubMed - indexed for MEDLINE]
Masked deficit of vitamin B12 in the patient with heterozygous beta-thalassemia and spastic paraparesis.

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The spinal cord, brain, optic nerves and peripheral nerves may be affected by vitamin B12 (cobalamin) deficiency. Deficiency of vitamin B12 also causes megaloblastic anaemia, meaning that the red blood cells are usually larger than normal. In this paper we report a 16-year old girl who was referred to us for the evaluation of mild paraparesis and paresthesias marked by tingling "pins and needles" feelings and general weakness. The patient, her parents and sisters were on a strict vegan diet, which made us believe that vitamin B12 deficiency may be the possible cause of the neurologic clinical manifestations. The serum level of vitamin B12 was low, but there was no macrocytosis in the routine blood examination. The electrophoresis of haemoglobin was pathologic, there was 3.7% of HbA2 and 11.6% of HbF (heterozygous form of beta-thalassaemia). When megaloblastic anaemia occurs in combination with a condition that gives rise to microcytic anaemia, many megaloblastic features may be masked. Instead of being macrocytic, the anaemia could be normocytic or even microcytic. Vitamin B12 deficiency is a diagnosis that must not be overlooked. This case report turns the light on the fact that increased MCV is a hallmark in vitamin B12 deficiency, but it is not an obligatory sign.

Publication Types:

- Case Reports
- Research Support, Non-U.S. Gov't

PMID: 15742609 [PubMed - indexed for MEDLINE]