Cobalamin Deficiency, Methylation and Neurological Disorders

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An article in the New England Journal of Medicine from 1988 drew the attention to a scant discerned problem: neuropsychiatric disorders due to vitamin B_{12} (cobalamin) deficiency occured in patients, mainly elderly, who didn't present with hematological deviations.[1] After administration of vitamin B_{12}, the symptoms disappeared in practically all patients. The research demonstrated that in daily practice a deficiency of vitamin B_{12} is often not recognized as the cause of severe and frequently occuring psychiatric disorders. Advanced research confirmed these results.[2] Other research points out the danger of undiagnosed vitamin B_{12} deficiency, especially in pernicious anaemia.

B_{12} Status and Pernicious Anemia

Pernicious anemia is an autoimmune disease with the principle characteristic being that the stomach is not able to produce intrinsic factor necessary for adequate resorption of vitamin B_{12} from food. The disease shows a megaloblastic blood picture as a result of a chronic lack of vitamin B_{12}. Suprisingly, the research shows only a slight connection between low vitamin B_{12} status and pernicious anaemia.[3] Yet vitamin B_{12} blood levels are important for the diagnosis of pernicious anaemia. For this reason pernicious anaemia is often missed. Furthermore, a correct diagnosis is hindered by the rather aspecificity of vitamin B_{12} deficiency, and such a deficiency manifesting itself over the long term. Also the general opinion that storage of this vitamin in the human body is sufficient to supply it for three to six years does not help in diagnosing pernicious anemia adequately.

The first symptoms of a cobalamin deficiency are paleness and fatigue. In general, deficiency is diagnosed on the observation of enlarged red blood cells (macrocytosis). However this symptom cannot be distiguished from folate deficiency. The general opinion is that distinction usually only manifests after several years, when neuropsychiatric symptoms come forward: tingling hands and/or feet (always symmetrical), boredom, fatigue and lethargy, shortness of breath, palpitations, sore mouth with a thick, often painful tongue. Frequently a pale complexion with soft yellow discoloration (because of a deteriorated liver function) is seen. Irritability, loss of memory, mild depression and mood swings can also be observed.

B_{12} Deficiency and Alzheimer's Disease

New methods to assess vitamin B_{12} status show that vitamin B_{12} deficiency occurs much more often than was previously assumed.[4] Assessment of the methylmalonic acid level is a precise method to determine possible existence of vitamin B_{12} deficiency, if necessary supported by assessment of homocystein and cystathionin.

When these assessments are performed in elderly people, high percentages are often found, which indicates the existence of deficiencies of the vitamins cobalamin, folic acid and pyridoxal phosphate (vitamin B_6) in the elderly.[5]

Ten percent of all people between 65 and 75 years old, 20% of those between 75 and 85 years old and 30% of all those over 85 years old suffer from some sort of dementia.[6] The literature provides extended information on the deteriorated vitamin B_{12} status in patients with senile dementia of the Alzheimer type (SDAT). Van Tiggelen described subnormal levels of vitamin B_{12} in the cerebrospinal fluid

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of SDAT patients, in spite of normal serum levels.[5,7] Later others described B_{12} anomaly in SDAT patients.[8,9] To clarify connections mentioned above one should first gain some insight into the reactions of methylation (Figure 1)[10]

Methylation

In the body cobalamin is active in two forms. As adenosylcobalamin, a cofactor of the enzyme methylmalonyl-CoA-mutase, or as methylcobalamin, a cofactor of the enzyme methionine synthase.

The first form (adenosylcobalamin) is involved in conversion of methylmalonyl-CoA (MM-CoA) into succinyl-CoA. In case of shortage of vitamin B_{12} this conversion takes place insufficiently and a different conversion takes place of MM-CoA, namely in methylmalonic acid (MMA). A raised MMA-level can serve as an exclusive rate of vitamin B_{12} deficiency. This conversion is particularly important in the brain and is known as the propionate metabolism.[11,12]

The second form of vitamin B_{12} (methylcobalamin) is co-enzyme of methioninesynthase. This is an important enzyme in the reaction which transfers a methyl group from 5-methyl tetrahydrofolate (5-MTHF) to homocysteine, forming methionine. This reaction is the key reaction of the so called methylation, a series of reactions in the body transferring methyl groups. In these reactions S-adenosyl methionine (SAM) is used as methyl donor by methyltransferase enzymes. SAM is synthesized from methionine.[11,12]

Methylation is Part of Many Processes

Methyltransferases take part in a large number of body processes, including regulation of protein structure, regulation of DNA expression, production of phos-pholipids, and production of certain hormones and neurotransmitters.[10] There are also indications that methylation of phospholipids is the common mechanism of receptor signalling across cell membrane.[13]
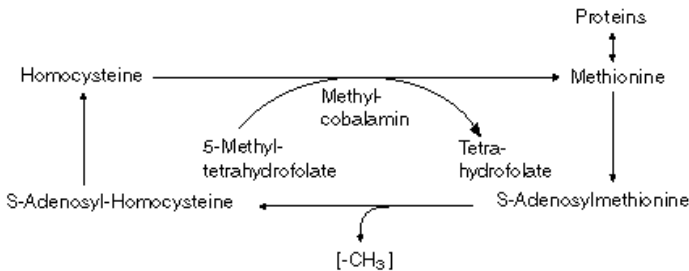
Methyltransferases transfer a methyl group away from S-adenosylmethionine (SAM) forming S-adenosyl-homocystein (SAH). SAH is a strongly competitive inhibitor of methyltransferases and accumulation of SAH in the cell will inhibit methylation reactions. The ratio between these two compounds is called the methylation ratio. A low ratio indicates inhibition of methylation.

SAH is broken down by S-adenosyl-homocysteinhydrolase into homocysteine and adenosine. Adenosine is rapidly metabolised into, for example, inosine. Homocysteine has three elimination pathways: remethylation to methionine (the main elimination route), breakdown to cystathionine or excretion from the cell.

Remethylation in the Brain

Remethylation of homocysteine is possible in two ways. The first is by way of the above mentioned enzyme methionine synthase, but remethylation can also take place by way of the enzyme betaine methyltransfersase. This enzyme is present in only a few organs, such as liver and kidneys

Figure 1. The Methylation Process

[-CH₃]

and is not present in the brains. In this case methylation reactions depend totally on functioning of methionine synthase.[10]

When both remethylation pathways fail, homocysteine is converted with difficulty into cystathionine , and cysteine because the regulating enzyme is activated by high levels of SAM, and these are lacking. Consequently SAH and homocysteine accumulate, the ratio between SAM and SAH (methylation ratio) is low and methylation is inhibited.[10] The brain is capable of remethylation of homocysteine exclusively by way of methionine synthase and in case of disfunctioning methionine synthase enzyme is totally dependent on plasma methionine supply, derived from food or from organs such as the liver, which has the disposal of an alternative synthesis pathway. If this supply also fails, clinical symptoms manifest.

Neuropathy Caused by B$_{12}$ Deficiency

Neuropathy as a complication of cobalamin deficiency is characterized by demyelinisation of the posterolateral nerves of the spine. At first it was thought to be due to a disturbance of the enzyme methylmalon-CoA-mutase. Shortage of adenosylcobalamin may inhibit the enzyme, which may result in production of abnormal fatty acids. Incorporation of these defective fatty acids in myelin may lead to demyelination.[14]

Recent evidence however points to a mechanism by way of the enzyme methionine synthase by methylcobalamin. The most important proof of this is derived from experiments with nitrogen oxides. Nitrogen oxides are strong inhibitors of the enzyme methionine synthase. They inactivate methylcobalamin by oxidation of monovalent cobalt groups to cobalt oxide, which then forms biological inactive cobalamin analogues. Exposure to nitrogen oxides (also in anaesthesia) results in neuropathy in humans, primates, fruitbats and pigs.[15] In cerebrospinal fluid and neural tissue of these animals extremely low ratios of SAM to SAH are found after exposure to nitrogen oxides. Adequate supply of methionine appears to be able to prevent neuropathy at least partly.[15] The addition of S-adenosyl methionine itself appears in several studies to have many beneficial effects on the central nervous system, especially on the monoamine neurotransmitter metabolism and receptor systems. Provision of these methyl donors is responsible for the remyelination observed in patients with inborn disorders of folic acid metabolism and methylation.[16]

Affected Liver is an Extra Risk Factor

In patients with affected liver function, such as in alcoholics, chronic phenytoin users and patients exposed to hepatotoxic chemicals with neurotoxic potential, abnormally low levels of cobalamin are found in cerebrospinal fluid.[7,17] This could be indicative of an abnormal conversion of neurologically active cobalamin by the affected liver, for example by changed activity of microsomal liver enzymes.[18-20] In patients with predominantly neurological symptoms of cobalamin deficiency, higher serum levels of cobalamin analogues are found than in patients with hematological symptoms.[21] This finding is supported by data derived from studies of alcoholics.[22]

Interaction with Thiamine Metabolism

It is possible that functional vitamin B$_{12}$ deficiency blocks resorption, transport and biological activity of thiamine. In particular, methylcobalamin deficiency could induce reduction of the intestinal alkaline phosphatase level, blocking intestinal resorption and possibly also biological activation of thiamin.[23,24] Deficiency of biological active thiamine in the brains is connected with a range of neurological diseases, as is known from brain research in chronic alcoholics.

Folic Acid

Folate deficiency is common in elderly. Research among 1250 randomly selected

elderly persons showed that 8% had low serum folate levels.[25] Alcoholics, too, run a higher risk of folate deficiency because alcohol specifically affects the formation of tetrahydrofolate. At first, effects of folate deficiency are indistinguishable from vitamin B_{12} deficiency. Differentiation between these deficiencies is possible only after a long period, when vitamin B_{12} deficiency is visible by degeneration of nerve tissue.

The biologically active form of folic acid in the body is 5-methyltetrafolate (5-MTHF), mentioned before as a methyl donor for the enzyme methionine synthase, that converts homocysteine to methionine. The body, as mentioned, has at its disposal alternative supply routes for methyl groups in case of insufficient supply of folic acid. But in longstanding folate deficiency these protective mechanisms, too, may fail and result in neurological disorders. Folic acid can act in methylation reactions in other ways. Several interactions are documented between vitamin B_{12} and folic acid, which suppose that folic acid, or rather 5-MTHF, plays a part in the conversion of cobalamin to methylco-balamin.[26] This theory is supported by clinical observations of patients with a neuropsychiatric syndromes which are responsive to folate. In research in elderly patients with depression associated with mild dementia, 5-MTHF supplements remedied symptoms in 45% of cases, compared to 29% in the control group treated with trazodone.[27]

In epidemiologic research psychiatric disorders such as depression, mania, schizophrenia, personality disorders and dementia are also connected with folate status. The main relationship was found with depression and schizophrenia.[25] This may be due to the fact that absorption of folic acid from the gastrointestinal tract is inhibited specifically by antidepressants and anti-epileptics.

Conclusion

Vitamin B_{12} deficiency is often not recognized as the root of neurological

syndromes and can occur without reduced serum level or hematological deviations. Assessment of the methylmalonic acid level is a specific and reliable method to determine vitamin B_{12} status. Elderly people often appear to have abnormal methyl malonic acid levels, which indicates disturbed methylation. Senile Alzheimer's dementia, too, is often accompanied by an affected B_{12} status.

The brain has available, in constrast to organs such as the liver, only one method to remethylate homocysteine to methionine. However B_{12} deficiency inhibits the enzyme responsible for this conversion, and the brain, therefore, becomes totally dependent on supply of methionine in the blood. When this supply fails, neuropathy, among other things, may develop. Folic acid as methyl donor is an important factor in methylation and also in converting vitamin B_{12} into a biological active form.

A complicating factor when the liver is affected by alcohol or toxic substances. As a consequence vitamin B_{12} is probably converted abnormally, through which biological inactive cobalamin analogues enter the bloodstream. Disturbance of vitamin B_1 metabolism may also contribute to development of neurological symptoms in vitamin B_{12} deficiency.

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