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Vitamin B12 and mercury

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A report of DUMEX-ALPHARMA, International Pharmaceuticals Division

(Vitamin-B12 as Methylcobalamin is now available as sublingual platelets)

Dear Member of the International MELISA Society,

Thank you very much for nice company at the Knappthof and for interesting lectures. Some of you have asked me to summarize my, maybe, somewhat confusing overview on vitamin B12. I shall try to do that.

The reason vitamin B12 is interesting in this context is that the symptomatology of mercury overload and of vitamin B12 deficiency to a great extent are very similar, sometimes almost identical and this might be not just a coincidence. Some of the well-known symptoms of vitamin B12 deficiency - other than anemia - are:

Depression, fatigue, concentration difficulties, weakness (often of the legs), memory impairment, personality changes, neuropathia, anosmia, incontinence etc.

You have probably encountered many of these symptoms in your "mercury patients".

How does vitamin B12 work?

Vitamin B12 is active as a coenzyme in mainly two enzymatic intracellular reactions. In one, the adenosyl B12 form mediates the conversion of methylmalonic coenzyme A to succinylcoenzyme A, a reaction connected to the citric acid cycle and thus of importance for the carbohydrate and lipid metabolism. Adenosylcobalamin constitutes the major intracellular pool of vitamin B12. A depletion of adenosylcobalamin results in an increase in the methylmalonic acid (MMA) concentration. As MMA diffuses out of the cell the levels in plasma or serum can be used to check the adenosyl B12- status. MMA is a specific but rather late marker for vitamin B12 deficiency.

The other reaction in which vitamin B12 is involved is the recycling of homocysteine into methionine in the so called methylation cycle (illustrated p. 19 in the enclosed brochure). In this methylation cycle methyl B12 bound to methionine synthetase (MS) interacts closely with folates in that it donates its methyl group to homocysteine which then forms methionine. Cobalamin then accepts a methyl group from methyltetrahydrofolate (methyl THF) to form THF, which participates in the synthesis of DNA.

Methionine is further converted into S-adenosylmethionine (SAM) by ATP. SAM is a very essential methyl donor in a lot of reactions - more than 100 enzymes have been identified so far, requiring SAM. SAM is i.e. involved in protein- and myelinsynthesis and is required in the metabolism of transmitter substances such as dopamine, serotonin, (nor)adrenaline and histamine. This explains why a vitamin B12-deficiency can manifest itself in so many different ways.

SAM does actually exist as a drug in some countries. It has been shown to be as effective as tricyclic antidepressive medicaments and also effective in fibromyalgia. However, there is a drawback as one risk accumulation of homocysteine. Therefore one should rather aim at optimizing the methyl B12/folate mediated recycling of homocysteine into methionine and SAM.

If the conversion of homocysteine to methionine (and SAM) does not work properly, homocysteine will accumulate in the cell from where it diffuses into blood. A methylcobalamin deficiency therefore induces a hyperhomocysteinemia. The homocysteine level is thus a marker of the methyl B12 status - but also for the folate status as there is such a close interaction between folate and methyl B12. This test is thus a less specific than MMA but an earlier marker for B12-deficiency as methyl B12 constitutes a minor part of the B12 pool (though it normally dominates in blood) and is first depleted in B12-deficiency.

However, the important recycling of homocysteine to methionine and SAM can be disturbed not only by vitamin B12, or folate deficiency.

Enzyme defects

Normally the enzymes in the methylation cycle are regulated by feedback mechanisms very accurately to meet the needs. If, however, an enzyme involved in the reactions is defective, the whole mechanism may be disturbed. It has recently been shown that congenital enzyme defects of i.e. methylene tetrahydrofolate reductase (MTHFR) are quite common. The consequence of a MTHFR-defect is that Vitamin B12 and folate cannot act properly - you get a functional vitamin deficiency in spite of normal levels of these vitamins. Between 10 and 19 % of a general population are homozygotes for a so called thermolabile MTHFR with a low to very low, enzyme capacity (several studies are available from different countries). Even the heterozygotes have an impaired enzymatic function.

A functional deficiency can however more or less be compensated for by giving larger doses of vitamin B12, and folic acid which optimize the available enzyme capacity.

It is interesting that two recent studies have shown that parents of children with NTD (neural tube defects) are homozygotes for the thermolabile MTHFR - more than three times more than in parents having normal children.

Maybe these enzyme defects are overrepresented also among your mercury patients making them more, vulnerable? In Sweden there is right now a study running to check if this defect is an overall risk factor - for death - in comparing the prevalence of the defect in newborns with the prevalence in 80-year-olds!

The diet is another factor that influences the methylation cycle. Large quantities of methionine from food (meat for instance) result in high levels of SAM- High levels of SAM downregulate MTHFR and MS (methioninsynthase) - even if their activity is already reduced. This results in - more or less - a block of the remethylation of homocysteine - which accumulates even though the transsulfuration pathway into cysteine is upregulated. When SAM is depleted, MTHFR and MS are again upregulated. A vitamin B12-deficiency gives the same result. (Maybe that's why one common symptom of B12 deficiency is aversion to meat?).

What has all this to do with mercury?

Well, there may well be some important links. The monovalent cobalt atom in methyl B12 is readily oxidized by various compounds - for instance nitrous oxide. This oxidation inactivates methioninsynthase (MS) which has then to be formed de novo. Mercury, as we know, does oxidize many compounds, logically also cobalt. If this hypothesis (which is about to be verified), is confirmed, it means that mercury can block the methylation cycle and thus induce a functional B12-deficiency (folates are not altered). This in turn is one explanation of why symptoms of mercury overload and vitamin B12-deficiency may be identical!

There is also a second possible interaction between vitamin B12, and mercury. Mercury has indeed been shown to impair the Transport of vitamin B12 over the blood-brain barrier which results in a low CSF/serum concentration ratio of the vitamin. Low CSF levels of vitamin B12 (and high CSF-homocysteine levels) have been observed in fibromyalgia (chronic fatigue syndrome), MS and in dementia. High doses of vitamin B12, that overcome the block to some extent, has had sometimes stunning results in these conditions.

How can you check if vitamin B12-status and the methylation cycle have been affected in your patients?

The availability of the new marker for functional methyl B12/folate activity, that is homocysteine levels in plasma, serum and/or CSF actually means a revolution. The analyses are not readily available yet everywhere - but they will be! (Four years ago there was only 1 lab in Sweden proposing it and then at a very high price. Today about 15 labs offer it for little more than SEK 100!)

A high homocysteine level means that something is wrong in the methylation cycle but not what is wrong. The reason might be a quantitative B12- or folate deficiency, or a functional deficiency due to a hereditary or mercury induced enzyme deficiency, or in the case of an isolated high CSF level, a mercury induced distribution deficiency. However it is not yet possible to verify if mercury is the underlying factor, although high mercury levels may indicate this. However, whichever the cause of the deficiency in the methylation cycle vitamin B12 and folate treatment may ameliorate the situation. Larger doses of vitamin B12 will promote, a passive diffusion (to the CSF) and will optimize the action of a deficient enzyme.

Which doses should one give and how often?

This is a tricky question, as you do not know how severe the deficiency is or how impaired the patient enzymes are. Therefore the best advice is to give a dose that is high enough, whatever the causes. You can do this as the toxicity of vitamin B12 is extremely low. There are no serious side effects ever reported with vitamin B12. The reason for this could be that there is kind of servo steering. The effect is limited by the enzyme capacity - which is wisely maximized not to hurt us. Therefore, one can give an aggressive treatment initially till the patient gets better. Subsequently the patient is a very good "biosensor" as he or she feels when another injection is called for! -You must bear in mind, that if you are treating a B12 deficiency syndrome, the chances of reversibility of the neurologic symptoms are smaller the longer the symptoms have been there. Often 6 months of intensive treatment are needed before one sees a substantial amelioration. However, some symptoms may respond very quickly - i.e. depression, fatigue and memory disturbances, which is logical considering the importance of SAM for the transmitter substances.

What preparation should you use?

In Europe there are two derivatives on the market; cyanocobalamin and hydroxycobalamin, in the US only the former. The reason of this is that these two forms are the easiest to synthesize! It would be more logical to use the coenzymes, that is methyl- and/or adenosylcobalamin. These products have been on the market - but never promoted - in southern Europe - the market being considered too small, as the sole indication until recently was pernicious anemia, that is absence of intrinsic factor affecting about 1% of the population over 60!

There is still methylcobalamin preparations in Portugal, but their documentation (quality) does not correspond to current requirements. In contrast to this methylcobalamin (Methycobal) is the leading derivative in Japan and this product is also well documented. It is going to be introduced in Sweden and hopefully subsequently in other European countries. The advantage of this derivative is that it replaces the most vulnerable form of vitamin B12 methylcobalamin - directly without having to rely on the whole transformation chain from cyano- or hydroxycobalamin (8 steps). Deficiencies in this chain may not be that rare. Moreover, there is an enzyme saturation level in the synthesis of the active coenzymes, above which the cyano- or hydroxycobalamin accumulates and then compete with the active forms at the binding sites, which may actually worsen the situation!

To summarize

I am obviously an incurable B12 fan - to the extent to bet (12 bottles of champagne) with any of you, that if you check the CSF levels of homocysteine/B12 in your typical "mercury patients" and compare them with the values from matched healthy controls without fillings, I am convinced that you will find significant differences with such a small sample as 15 + 15! That is, I am convinced that many mercury induced symptoms are secondary B12 deficiency symptoms! This, of course, does not mean that vitamin B12 is the answer to everything and it also depends on other vitamins for its action, as it interacts not only with folates, but also requires vitamin E for its action, which in turn requires vitamin C for its regeneration and so on. One should not forget vitamin B6 either, which is required to get rid of homocysteine by the transulfuration pathway, but one must first make sure that the methylation cycle is all right.

Actually one can induce a neuropathy in giving very large doses of B6 to healthy individuals!

Of course many other factors can also be affected by heavy metals, but I am convinced that the methylation cycle is crucial in this context.

By the way, do bear in mind that if you have a block in the methioninsyntase- activity and add vitamin B12, the plasma folate levels will decrease very fast as more intracellular - and active - THF will form! Thus, always add some folic acid as well to the treatment regimen even if the initial folate levels are normal.

In interpreting your homocysteine levels you should bear in mind that the reference levels for homocysteine are based on values from a general population - not necessarily a healthy general population and the upper reference limit is therefore often rather high.

It is shown that hyperhomocysteinemia is risk factor for cardiovascular disease and that the risk is concentration dependent and begins at 10-11 mmol/l! Homocysteine may also be cytotoxic - thus carcinogen - and embryotoxic.

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