B_{12} and cognition

What the guidelines don't say

by Henry Olders

DOES VITAMIN B_{12} play a role in cognitive functioning? No fewer than 110 studies (33 of them prospective) on more than 45,000 subjects have demonstrated an association between cognitive deficit or dementia, and homocysteine (Hcy) and/or B vitamins, which affect Hcy.[1] Those B vitamins are folate, B_6 and B_{12}. Unfortunately, there are also many intervention studies that fail to show improvement in cognition or dementia with supplementation of these 3 vitamins, even though Hcy decreases. What gives?

B vitamins in the elderly

In the elderly, high levels of Hcy and low-normal levels of folate, B_6 and B_{12} are common worldwide. For example, a recent study in Denmark showed that folate deficiency was present in almost one third of adults.[2] But in the U.S. and Canada, folate deficiency has become rare since food manufacturers began fortifying their cereal grain products with folic acid in 1998. According to the U.S. National Center for Health Statistics, "The prevalence of low RBC folate in the U.S. population 4 years of age and older declined from 30.4% in 1988-1994 to 2.8% in 1999-2000 and rates have remained low since that time."[3] As for vitamin B_6, the prevalence of deficiency in the elderly decreased even earlier, from 23.3% in 1988/89 to 5.7% in 1993 in one study of American and European populations.[4] B_6 deficiency is associated with seizures, migraine, chronic pain and depression,[5] but its relationship with cognitive impairment seems to be mediated through Hcy.

B_{12} mechanisms

That leaves B_{12}, or cobalamin. In addition to its effects on Hcy levels, B_{12} deficiency is thought to cause neurological problems through at least two other mechanisms. The first of these involves an enzyme that's dependent on the presence of B_{12}; failure of this reaction results in an increase in methylmalonic acid (MMA, which can be used as a test for B_{12} deficiency). MMA, when incorporated into myelin instead of normal malonic acid, destabilizes the myelin, causing demyelination. The second mechanism involves another B_{12}-dependent enzyme that regenerates methionine from homocysteine. The methionine is needed to make S-adenosyl-methionine (SAMe) is required for the production of the phospholipids that become part of the myelin sheath — essential for the proper functioning of the nervous system. Wrapped around the axons of neurons, this sheath speeds up the transmission of nerve impulses. Its appearance gives rise to the term "white matter" of the brain.

Demyelination due to B_{12} deficiency can occur in the brain, in the spinal cord (where it's called "subacute combined degeneration") and in peripheral nerves. When it occurs in the brain, it manifests as cognitive impairment. It may be indistinguishable on MRI (T2-weighted) from the leukoencephalopathy seen in vascular dementia.[6,7] Fortunately, if recognized early and treated adequately, both the MRI changes and the cognitive problems are reversible. The key word here is "early": there is a window of opportunity during which treatment is effective, but after that, the damage becomes permanent.

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Prevalence of B_{12} deficiency

Unlike folate or B_6 deficiencies — usually caused by not getting enough of the right foods — B_{12} deficiency in seniors occurs most frequently because of impaired absorption, even when the diet contains adequate amounts of the vitamin.[8] And the conditions that cause this impaired absorption are on the increase. As a consequence, B_{12} deficiency has been found to affect 12% of the elderly; when the more specific MMA test is used, estimates rise to 24% and 46% among free-living and institutionalized elderly, respectively in the UK.[9] Unfortunately, even though widespread, it often goes unrecognized because its symptoms are seen in other conditions that frequently affect the elderly.

Causes of deficiency

B_{12} is found in meat and meat products, so vegans and to some extent other vegetarians are at risk of inadequate intake, as are elderly on a "tea and toast" diet. In food, B_{12} is bound to protein, and stomach acid is necessary to cleave it from the protein and make it available for absorption. Conditions decreasing gastric acidity, such as type 2 diabetes or gastric surgery, may thus impair B_{12} absorption, as can long-term use of medications for hyperacidity or gastro-esophageal reflux (e.g. pantoprazole or cimetidine). Infection with *H. pylori* can also reduce stomach acid. The global prevalence of infection is more than 50%.

Once cleaved from the food protein, B_{12} is picked up by another protein, called intrinsic factor, produced by cells in the lining of the stomach. When these parietal cells are destroyed by an autoimmune process, the resulting illness is called pernicious anemia, which used to be uniformly fatal. Gastric surgery can also cause B_{12} deficiency if the parietal cells are removed.

When the bowel slows down (as in patients taking opioid pain medication, or those with diabetes or scleroderma) bacterial overgrowth occurs. These bacteria may extract the available B_{12}, causing a deficiency in the host.

Any B_{12}-intrinsic factor complex that clears these hurdles then has to be absorbed in the terminal portion of the ileum. Surgical removal of that portion of the small bowel can thus cause B_{12} deficiency, as can various diseases that impair small bowel functioning, such as Crohn's disease or celiac sprue (gluten intolerance). Rarer causes include tapeworm infestation and nitrous oxide anesthesia. There are also a variety of genetic disorders affecting transport proteins that can result in B_{12} deficiency.

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How often does B_{12} deficiency cause cognitive impairment?

With such a complicated absorption pathway, it's no wonder that B_{12} deficiency is so common. But not all cases of deficiency manifest cognitive impairment. What percentage do? The short answer: we don't know.

To find out, we'd need to sample a specific population, for example community-dwelling elderly; do lab and cognitive function testing on the sample to find a cohort with neither B_{12} deficiency nor cognitive impairment; follow this cohort over a time period; retest periodically, i.e. at 6-month intervals, to identify co-occurring new-onset B_{12} deficiency *and* new-onset cognitive impairment; and finally, treat with B_{12} to see what percentage of cases show improvement. To my knowledge, no such study has ever been reported.

Problems with B_{12} testing

Even before undertaking such a study, a number of thorny issues would have to be addressed. Testing for B_{12} deficiency is prob-

lematic. It's generally agreed that blood or serum B_{12} levels may not reflect tissue levels, and can show normal or even elevated values in some cases of confirmed B_{12} deficiency (if the patient has a myeloproliferative disease,[10] or harbours gut bacteria producing inactive B_{12} analogues, or in some liver cancers). To overcome this, additional tests such as Hcy or

There is only a small "window of opportunity" during which cognitive impairment due to B_{12} deficiency can be successfully treated

MMA levels can be requested to increase overall sensitivity, but Hcy may be normal if the patient is getting adequate amounts of folic acid, and both Hcy and MMA may be elevated in renal disease. MMA testing remains expensive and is limited in availability, as is a more recent test, holotranscobalamin II (holoTC).

Detecting cognitive impairment

The detection of cognitive impairment is even more problematic, as it's based almost exclusively on tests and questionnaires that are sensitive to educational level, language, culture, the degree of training of the individual administering the test, whether or not the patient is depressed, even on the time of day! What's more, the capacity of tests to distinguish between the multiple types and degrees of cognitive impairment is quite limited, particularly at the mild and severe ends of the spectrum.

Treatment troubles

In terms of treatment, neither the dose, frequency, route of administration, or chemical form of B_{12} has been standardized. For example, cyanocobalamin (the only injectable form of B_{12} available in Canada) may be ineffective in heavy smokers who inhale cyanide from tobacco smoke.[11] And while the dose and frequency of injections needed to reverse the hematological manifestations of pernicious anemia is well known (1,000 µg intramuscular per month), it's possible that more frequent injections are necessary for improvement of cognitive symptoms. This is because individuals who lack intrinsic factor lose an appreciable portion of their B_{12} stores through failure of the so-called enterohepatic circulation (in which B_{12} and various inactive look-alike substances are secreted in the bile; only active B_{12} is normally reabsorbed via intrinsic factor, thereby purifying body stores of B_{12}).[12] Dietary pectin may also increase fecal losses.[13]

Recent evidence shows that many elderly persons respond poorly to daily oral doses under 500 µg, even if they don't have classical malabsorption.[14]

What's more, a number of reports suggest that there is a "window of opportunity" during which cognitive impairment due to B_{12} deficiency can be successfully treated; this window may be as little as 6 months after onset of symptoms.[15] If treatment is delayed beyond that point, response is unlikely.

Guessing game

Because the definitive research on the prevalence of cognitive impairment due to B_{12} deficiency has not yet been done, we need to look at other data to get an estimate. Back in the days when pernicious anemia was recognized and could be treated, at first with large amounts of raw liver and later with B_{12} injections (1928-1960), a series of reports described patients whose psychiatric and cognitive symptoms were improved with treatment.[16] In 371 pernicious anemia patients, a total of 117 conditions responsive to treatment were noted, including 19 with delirium and 54 with slow cerebration, confusion or memory loss. This represents just under 20% of those with severe B_{12} deficiency who also had hematological findings.

It's known, however, that B_{12} deficiency can cause neurological problems even in the absence of hematological findings.[17] This is especially likely since 1998, when mandatory fortification of foods with folic acid was begun in the North America. Folic acid can reverse the megaloblastic anemia of B_{12} deficiency (the so-called "masking" effect)[9] while doing nothing, or possibly even making things worse, on the neurological side.[18]

Taking B_{12} seriously

Although we know that B_{12} deficiency is common in seniors, and that it can cause cognitive impairment, clinicians continue to ignore B_{12} when memory problems manifest. Why?

One reason is that once dementia has set in, it's typically irreversible. So even if the cause was B_{12} deficiency, treatment with the vitamin changes nothing. This has led to the often-repeated statistic that less than 1% of dementias are reversible,[19] which many clinicians take to mean that lab testing is a waste of time and money. As a result, only 20% of primary care patients with suspected memory impairment or dementia are likely to get tested for B_{12}.[20] Take cognitive impairment seriously, early in its course, while it may still be treatable.

B_{12} tends to be downplayed in "official" guidelines. For example, in the Recommendations of the 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia, B_{12} is mentioned only once, in a recommendation to not administer it to persons suffering from AD who aren't deficient; cobalamin is not mentioned at all, while the obscure abbreviation "Cbl" (never defined) is included in a section on lab tests.[21]

Even when B_{12} deficiency is suspected, laboratory testing to confirm it remains problematic, as discussed above. My personal experience with the more specific MMA test is illustrative: over some 15 years of ordering MMA levels for elderly patients in whom I suspected B_{12} deficiency, not once did I get back an abnormal result! Given that over 30% of seniors in a number of studies have high MMA values, getting 100% normal values for my patients seemed statistically improbable. I discovered eventually that the reference range being used by our lab (which at the time apparently served all of Quebec for MMA testing) was intended to pick up a potentially fatal genetic disorder affecting infants — methylmalonic

TABLE 1

Symptoms, signs and risk factors for B_{12} deficiency

Symptoms

- fatigue
- leg weakness or paresthesias, unsteady gait, falls
- swallowing difficulties, sore tongue, weight loss, diarrhea
- severe depression[42]
- excessive sleepiness[43]
- incontinence[44]

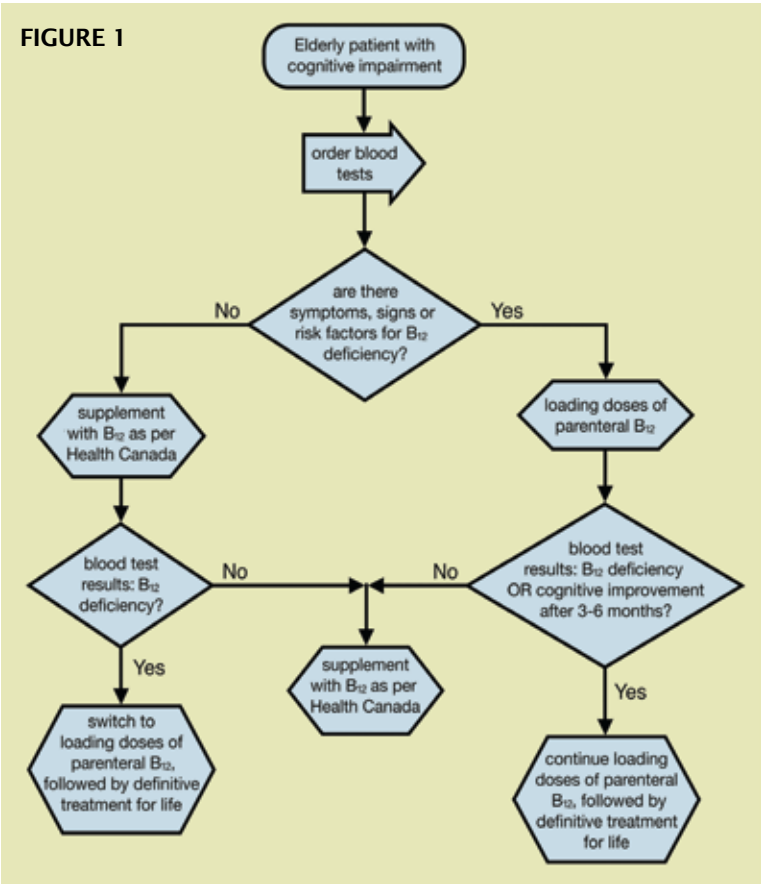
Signs

- anemia (typically megaloblastic, but because B_{12} deficiency and iron deficiency often occur together,[45] patients can develop anemias with a range of red cell sizes)
- paranoia, hallucinations, delusions ("megaloblastic madness")
- decreased bone mineral density (osteoporosis)[46]
- orthostatic hypotension[47]
- delirium

Risk factors

- age
- long-term use of proton pump inhibitors (usually prescribed for gastro-esophageal reflux disease, or GERD)[48]
- diabetes (especially patients taking metformin)
- *H. pylori* infection[49]
- opioid use
- other conditions that slow gastric emptying or bowel transit
- untreated celiac disease (gluten intolerance)[50]
- gastric or small bowel surgery
- tea and toast diet, vegan diet
- surgery with nitrous oxide anesthesia or exposure to nitrous oxide[51]
- cigarette smoking[52] as well as those exposed to cigarette smoke ("passive smoking")[53]
- diseases affecting absorption: Crohn's

FIGURE 1



aciduria. The lab was willing to change its cut-off value to that commonly used in research for detection of B_{12} deficiency, and I'm now getting lab results back that I feel I can rely on.

Patients with cardiovascular disease are likely to have cognitive deficits ascribed to vascular dementia. White matter hyperintensities on MRI are also likely to be ascribed to cerebrovascular disease, even though demyelinization from B_{12} deficiency can produce identical-looking lesions on T2-weighted MRI.

What should clinicians do?

First, aim to detect memory problems and cognitive problems early on. A useful screen is to ask family members "Does your mother/father/etc. ask the same question more than once?"; "Are they misplacing or losing things more often?"

Second, cultivate a high index of suspicion for B_{12} deficiency when cognitive problems first present. Ask about other symptoms that may be caused by B_{12} deficiency, look for other signs, and consider risk factors (Table 1).

Third, order appropriate lab tests. B_{12} levels are problematic, as previously discussed. Patients with near-normal creatinine values should also have tests for Hcy and MMA. In these days of folic acid fortification, elevated Hcy strongly suggests B_{12} deficiency. If available, holoTC testing may be a better alternative.

Fourth, if there are signs, symptoms or risk factors for B_{12} deficiency other than the cognitive problems, don't wait for the lab results to begin definitive treatment. Once bloods have been drawn, B_{12} can be given in loading doses intramuscularly or subcutaneously. A frequently employed regimen calls for 1,000 µg daily for 7 doses, followed by 1,000 µg weekly for 4 doses. After that, switch to oral administration, 1,000 µg once or twice daily. Although starting initially with oral B_{12} is recommended by some, because it is enough to reverse megaloblastic anemia, I recommend starting with parenteral B_{12} to quickly re-establish body stores and maximize the possibility of neurological improvement (which is time-sensitive). Even when B_{12} absorption is functioning well, only a small percentage of a 1,000 µg oral dose will be absorbed — the intrinsic factor absorption becomes saturated at less than one microgram, while the passive absorption is believed to be only around 1% of the oral dose.[22]

If Hcy and MMA tests both come back normal (i.e. no B_{12} deficiency) you can switch from B_{12} treatment to B_{12} supplementation, following the Health Canada recommendation: "Because 10 to 30 percent of older people may malabsorb food-bound vitamin B_{12}, it is advisable for those older than 50 years to meet the RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}."[23] In Canada, this means

that each adult > 50 should take a supplement, as B_{12}-fortified foods aren't available. Keep in mind that the elderly may need oral doses of at least 500 µg/day, even when there's no absorption problem.[14]

Lastly, assess the effect of your intervention on cognition. It may take 3-6 months to see a result.

Is treatment worthwhile?

There's no shortage of case reports and case series of patients whose cognition recovered completely[24-26] or improved considerably[24,27-33] with B_{12} treatment. What I find particularly interesting are case reports in which an objective marker of cerebral dysfunction, cerebral leukoencephalopathy on T2-weighted MRI, was found to markedly regress with B_{12} treatment.[34,35]

In contrast, therapeutic trials have generally had negative or at best, weakly positive results. Some examples follow.

In memory clinic patients, those with low B_{12} levels were treated and later reassessed. Dementia patients did not improve, but frontal lobe and language function improved in those with cognitive impairment.[36]

Supplementing for two months with 1 mg cyanocobalamin and 5 mg folic acid daily in 33 consecutive dementia patients led to improved scores on the MMSE and on tests of memory function, attention, and processing speed in the subgroup of 17 patients with mild/moderate dementia and elevated homocysteine level.[37]

A test group of 28 nursing home residents with dementia and low B_{12} levels were treated with 1,000 µg B_{12} IM daily for 7 days and then weekly for a total of 16 weeks of treatment. Compared to 28 dementia patients without low B_{12} levels, the test group showed nonsignificant improvements in scores on the Dementia Rating Scale (DRS) and the Brief Psychiatric Rating Scale.[38]

An open-label study of B_{12} treatment for 6 months in 18 older subjects with low B_{12} levels and cognitive impairment led to improvement on DRS scores for 11 out of the 18. Duration of cognitive dysfunction strongly predicted improvement, with patients symptomatic for less than 12 months gaining 20 DRS points on average, while those with more than 12 months of symptoms losing 3 points.[39]

Seventeen out of 36 consecutive patients, aged 16 to 80, with B_{12} deficiency neurological syndromes were found to have low MMSE for their education level. After 3 months of B_{12} injections, MMSE score improved in all, becoming normal in 29 patients.[40]

A recent meta-analysis[41] concluded "The evidence does suggest that oral vitamin B_{12} treatment is not effective for improving cognitive function. However, a potential effect of vitamin B_{12} when given intramuscularly cannot be excluded."

Carpe diem

Some cases of cognitive impairment are caused by vitamin B_{12} deficiency. For the B_{12}-cognitive impairment connection to make any difference, we need to discover the cognitive impairment early on in its course, as delayed treatment is unlikely to be helpful. As per the flowchart in Figure 1, obtain lab tests (B_{12} level, Hcy, MMA, and creatinine; holoTC instead of Hcy and MMA, if available). If other symptoms, signs, or risk factors (Table 1) point toward B_{12} deficiency, commence definitive treatment (after bloods have been drawn) with loading doses of parenteral B_{12} (1,000 µg daily for 7 doses, then weekly for 4 doses). If there's little to suggest B_{12} deficiency, then B_{12} supplementation (500 or 1,000 µg by

Treatment needs to be continued indefinitely. Unless we know for sure what caused the deficiency in the first place, we can't guarantee that it won't recur

mouth or sublingually, daily) carries little risk. If the blood test results come back indicating a deficiency, switch to the loading dose regimen; after the fourth weekly parenteral dose, switch to 1,000 µg by mouth twice daily, or continue with monthly injections of 1,000 µg. You may need to give injections more frequently if the underlying problem is intrinsic factor related (i.e. pernicious anemia, gastric surgery or atrophic gastritis). After 3-6 months of treatment, reassess cognition.

If there was a lab-confirmed B_{12} deficiency, or improvement on cognition with B_{12} treatment, inform the patient and the family that treatment needs to be continued indefinitely. Unless we know for sure what caused the deficiency in the first place, we can't guarantee that it won't recur. In other cases, continue B_{12} supplementation for adults > 50, as recommended by Health Canada.

Follow the above protocol, and your reward, with some of your patients, will be their appreciation and that of their families for taking away the spectre of irreversible dementia and giving them back their lives. PE

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