Memorandum

To: All physicians

From: Henry Olders, MD

Date: 2007-7-25

Subject: Methylmalonic acid test reference range

As you are aware, the hospital has adopted a protocol for Vitamin B12 treatment that requires laboratory confirmation of a B12 deficiency. I have stated my position that this is bad medicine, as it eliminates the role for clinical judgment and experience in decisionmaking, in an area where the risk of harm from overtreatment is essentially zero, while the risk of not treating or not treating adequately, or not treating quickly enough when there is neurological impairment, is permanent disability for the patient.

Nevertheless, it is important to screen new patients for vitamin B12 deficiency, and to use specific tests where appropriate. The medical literature has long recognized that methylmalonic acid (MMA) testing in patients with normal creatinine levels is more sensitive for identifying tissue deficiencies of B12, than the test for plasma B12 level; it is also more specific than the other frequently used metabolite level, homocysteine, which is also sensitive to folic acid and vitamin B6.

Unfortunately, MMA testing in Montreal has not proved very helpful in identifying B12 deficiencies. During the past 10 years, I have requested MMA levels on well over 100 patients; not once did the MMA report indicate a value out of the normal range. Statistically, for these elderly people, I should have found high MMA levels for 15 to 25% of cases, at least; however, not even when the B12 level itself was clearly low, and even the homocysteine level was elevated, was the MMA level abnormal. I concluded that the MMA test itself was unhelpful, and stopped ordering it.

Recently I had occasion to revisit this issue. A patient on one of the medical units was found to have a B12 level of 68 (N > 135 pmol/L), a homocysteine level of 53.6 (N < 12 micromol/L) and an MMA of 0.68 (N < 1.0 micromol/L). Again, the MMA level being normal in this situation did not make sense.

With the help of Mme Pauline Bourbonnais of our lab, I was able to contact biochemist Dr. Marc Martin at Sacré-Coeur, who indicated that in fact MMA levels were not done at his lab, but were sent to a McGill research lab. He directed me to Dr. Orval Mamer, head of the the mass spectrography lab at McGill, which has been doing the MMA determinations for both McGill and U. Of Montreal hospitals.

Dr. Mamer told me that the reference range for MMA used by his lab (< 1.0 micromol/L) was designed to screen for methylmalonic aciduria, a genetic disorder affecting children. I subsequently provided him with information about the reference ranges used for detection of B12 deficiency states from 16 recent articles (see http://tinyurl.com/yp7pgg)

and he will begin to provide MMA results with a new reference range, with 0.27 micromol/L as the upper limit of normal.

I asked our lab to provide me with a list of MMA results for the past couple of years. There were 47 results; the good news is that none of these were above 1.0, meaning that none of the tested residents appear to have the genetic disorder methylmalonic aciduria!). However, 22 out of the 47, or 46.8%, were above 0.27 micromol/L, indicating a B12 deficiency (if the creatinine were normal). Eleven out of the 22 (50%) with elevated MMA have died, compared to only 2 out of 25 (8%) of those with normal MMA levels. Thus, if nothing else, MMA may help to predict early mortality.

Bottom line: with this new reference range information, MMA levels can be considered a useful way to diagnose B12 deficiencies. However, it remains an expensive test.

On the horizon is a newer test, called holoTranscobalamin (this refers to a B12 transport protein) which is much less expensive to do, and may provide even greater accuracy than MMA for detecting B12 deficiency.

Below is the abstract of an article that I am writing on B12 deficiency in nursing home residents. It includes my recommendation for a protocol. As the article is set up as a wiki (http://tinyurl.com/3cqqcb), I encourage you to add your contributions or comments.

If you wish additional background on the role of B12 in the elderly, the slides of my talk on this subject are available here: http://tinyurl.com/298fae

Abstract

Vitamin B12 (cobalamin) deficiency is common in the elderly, with hospitalized patients and nursing home residents at higher risk than community-dwelling seniors. There can be serious neurological consequences of B12 deficiency which become irreversible if not treated early. Mandated fortification of flour with folic acid in the U.S. and Canada since the late 1990's is thought to increase the likelihood that B12 deficiency will remain undetected. Because the primary cause of deficiency in the elderly is malabsorption of food-bound cobalamin, a recommendation was made in 1998 by the U.S. Institute of Medicine in partnership with Health Canada, that every adult over the age of 50 should obtain a majority of the Recommended Daily Allowance (RDA) for B12 from supplements or from food fortified with B12.

The detection of B12 deficiency states using laboratory testing has always been problematic, with an unacceptably high level of false negative test results for the more commonly used tests (B12 level; homocysteine). Thus clinical detection of

B12 deficiency requires a high index of suspicion, since early manifestations are often subtle and easily attributable to a variety of other conditions.

The author proposes the following protocol or guideline to assist the clinician in the prevention, early detection, and treatment of B12 deficiency states in nursing home settings:

1. get baseline lab values when patients are first admitted;
2. look for early and subtle signs and symptoms of B12 deficiency in newly admitted patients;
3. if lab values demonstrate B12 deficiency, OR if there are signs and symptoms of deficiency, treat with therapeutic doses of B12 supplements.
4. after a suitable interval, assess the effect of the therapeutic B12 intervention. If there was a response, continue the intervention at therapeutic levels. If no response, switch to low-dose B12 supplementation.
5. if no deficiency on lab test or clinical grounds, commence low-dose B12 supplementation.
6. at least yearly, reassess for signs and symptoms of B12 deficiency (ie maintain a high index of suspicion). Doing routine screening blood tests will have a low yield at this point, because everyone in this elderly population will be on either therapeutic or low dose B12 supplementation.