Testing for Vitamin B12 Deficiency in the Elderly

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Abstract

Vitamin B12 deficiency affects around 20% of seniors, and can cause memory impairment and even dementia, which becomes irreversible if not treated quickly. Thus, diagnosing and treating suspected B12 deficiency quickly and accurately is important. Because B12 blood levels can be inaccurate for a variety of reasons, a more reliable test, methylmalonic acid (MMA), is often requested to diagnose B12 deficiency.

Over a number of years, it was observed that MMA tests for seniors both at Ste. Anne's Hospital and earlier at the Jewish General Hospital, had never come back as abnormal, even for those patients who clearly had B12 deficiencies as detected by other means. Even from a statistical point of view, one could have expected at least 20% to be abnormal.

In comparing the reference range for normal from the laboratory doing our MMA determinations, with the reference range usually used in research, it became clear that there was a large discrepancy. When this was corrected, MMA tests finally became useful, not only to Ste. Anne clinicians, but to all the McGill and University of Montreal affiliated hospitals as well.

Additionally, in reviewing older test results, a strong correlation was discovered between elevated MMA levels and mortality. Introduction

Introduction

Vitamin B12 deficiency is an important issue at Ste. Anne's Hospital:

- it affects 15 - 25% of seniors
- it can cause dementia, confusional states, paranoia
- can affect care needs by causing paralysis, incontinence
- if not detected and treated quickly, neurological impairments become permanent

Detecting B12 deficiency can be problematic because the usual test for blood B12 level is sometimes inaccurate.

A more specific test for B12 deficiency, "methylmalonic acid" (MMA) is available. However:

- it is not done in most hospitals (has to be sent out)
- more expensive
- results may take a month or longer

In my clinical experience with MMA testing over 10 years, with more than 100 patients, MMA results were always reported as normal, even when:

- other tests indicated a B12 deficiency
- patient symptoms suggested B12 deficiency
- symptoms improved with B12 treatment
- even in a random sample of seniors, at least 15% of MMA tests should have been abnormal

With these results, I and other clinicians at McGill had stopped using MMA tests, as they were unhelpful.

Objectives

- determine why MMA tests for our patients did not detect B12 deficiency
- if possible, correct the problem

Method

With help from Pauline Bourbonnais (Chef de service, laboratoire-radiologie) and Dr. Marc Martin (biochemist, Hôpital Sacré-Coeur), MMA testing was tracked to the Mass Spectrography Laboratory at McGill University. This lab was doing MMA tests for all the McGill University and the University of Montreal hospitals.

Dr. Orval Mamer, lab director, explained that the reference range (range of normal values) for MMA used at his lab, < 1.0 micromol/L, was intended to detect "methylmalonic aciduria" (a potentially fatal genetic disorder usually diagnosed in infancy).

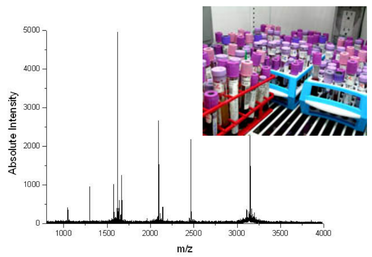
Dr. Mamer expressed willingness to revise his lab's range if indicated.

A literature search was performed to locate recent journal articles in which MMA reference range values for the detection of B12 deficiency, were stated.

A consensus value for the MMA reference range was determined.

The results of all MMA testing done for Ste. Anne's Hospital patients were evaluated using this consensus value. Mortality status was extrapolated from patient status as entered in the hospital electronic medical records system. The probability of the association between MMA abnormality and mortality was calculated using Fisher's exact test (two-tailed) (http://www.graphpad.com/quickcalcs/contingency1.cfm)

Typical Mass Spectrogram



Results

Using PubMed, 16 recent articles were found which stated reference range values for MMA testing.

The consensus reference range from the articles was < 0.27 micromol/L MMA, for detection of B12 deficiency. This is less than one-third of the previously used range.

Our lab provided MMA test results for 47 patients, done between mid-2005 and mid-2007. These tests had been ordered when a B12 deficiency was suspected.

Out of the 47 tests, 22 were abnormal using the new reference range. Eleven of this group of 22 patents had died, compared to 8 out of 25 patients with normal tests (P = 0.0025).

MMA level	number of patients (%)	number deceased by July 2007 (%)	P
< 0.27 (normal)	25 (53.2 %)	2 / 25 (8.0 %)	
≥ 0.27 (abnormal)	22 (46.8 %)	11 / 22 (50.0 %)	0.0025
Total	47 (100 %)	13 / 47 (27.7 %)	

Discussion

When the appropriate reference range was used, MMA test results were abnormal in almost half of the cases where vitamin B12 deficiency was suspected.

Abnormal MMA values appear highly predictive of increased mortality.

The new reference range value was used when MMA results are reported, not only for Ste. Anne's Hospital patients but for all MMA tests ordered from McGill and U. of Montreal hospitals.

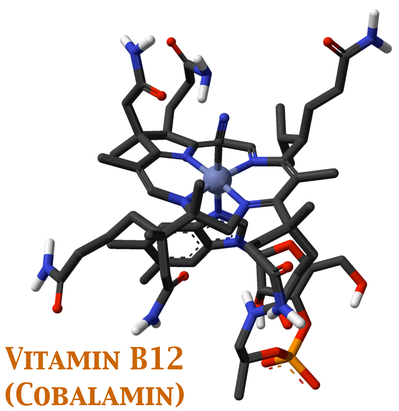
Limitations: small sample, nursing home residents, most very elderly (>80 years), only males.

Conclusions

If you consistently fail to get expected results with laboratory tests, examine the underlying assumptions.

Methylmalonic acid (MMA) testing with an appropriate reference range (<270 nmoles/L) detects abnormalities in about half of elderly male patients suspected of having a B12 deficiency.

An abnormal MMA result appears to predict increased mortality in this sample. This finding warrants further investigation.



Vitamin B12 (Cobalamin)

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Bibliography for MMA Reference Range

Clarke R, Sherliker P, Hin H et al. Detection of vitamin B12 deficiency in older people by measuring vitamin B12 or the active fraction of vitamin B12, holotranscobalamin. Clin Chem. 2007;53:963-970.

"definite metabolic vitamin B12 deficiency (defined as MMA >0.75 micromol/L) or probable metabolic vitamin B12 deficiency (defined as MMA >0.45 micromol/L)"

Garcia AA, Haron Y, Evans LR, Smith MG, Freedman M, Roman GC. Metabolic markers of cobalamin deficiency and cognitive function in normal older adults. J Am Geriatr Soc. 2004;52:66-71.

"Normal values in this laboratory for the biochemical parameters were Cbl 165-740 pmol/L, RBC folate 200-1300 nmol/L, MCA 60-228 nmol/L, tHcy 5.1-13.9 nmol/L, and MMA 73-271 nmol/L."

Herrmann W, Schorr H, Obeid R, Geisel J. Vitamin B-12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr. 2003;78:131-136.

"Normal MMA ≤ 271 nmol/L"

Hvas AM, Nexo E. Diagnosis and treatment of vitamin B12 deficiency--an update. Haematologica. 2006;91:1506-1512.

"MMA reference interval: 0.08-0.28 µmol/L; Gray area: 0.29-0.75 µmol/L; >0.75 µmol/L B12 deficient"

Johnson MA, Hawthorne NA, Brackett WR et al. Hyperhomocysteinemia and vitamin B-12 deficiency in elderly using Title IIIc nutrition services. Am J Clin Nutr. 2003;77:211-220.

"The previously determined normal ranges were 73-271 nmol/L for MMA (24)"

McCracken C, Hudson P, Ellis R, McCaddon A. Methylmalonic acid and cognitive function in the Medical Research Council Cognitive Function and Ageing Study. Am J Clin Nutr. 2006;84:1406-1411.

"Likely metabolically significant" vitamin B-12 deficiency was defined as an MMA concentration greater than the laboratory upper limit of normality (0.42 micromol/L) in the absence of significant renal impairment (creatinine <120 micromol/L)."

Morkbak AL, Hvas AM, Lloyd-Wright Z et al. Effect of vitamin B12 treatment on haptocorrin. Clin Chem. 2006;52:1104-1111.

"The population with suspected deficiency was recruited from 937 individuals with suspected vitamin B12 deficiency [based on methylmalonic acid (MMA) concentration greater than or equal to 0.28 micromol/L within the past 4 years] (14)."

Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 2007;85:193-200.

"We defined elevated MMA as a serum MMA concentration above the recently published reference range (ie, 60-210 nmol/L) for serum vitamin B-12-replete survey participants with normal serum creatinine concentrations (32). It should be noted that a similar strategy applied to data from the previous NHANES led to a cutoff point of 370 nmol/L (33)."

Nilsson K, Gustafson L, Hultberg B. Improvement of cognitive functions after cobalamin/folate supplementation in elderly patients with dementia and elevated plasma homocysteine. Int J Geriatr Psychiatry. 2001;16:609-614.

"The upper reference limit (95th percentile) for plasma homocysteine in an elderly population is 19.9micromol/L (Nilsson et al., 1994) and that for plasma methylmalonic acid was 0.41 micromol/L (Nilsson et al., 1997)."

Pfeiffer CM, Caudill SP, Gunter EW, Osterloh J, Sampson EJ. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999-2000. Am J Clin Nutr. 2005;82:442-450.

"For plasma tHcy and MMA, the reference ranges for serum vitamin B-12-replete participants with normal serum creatinine concentrations were 3.2-10.7 micromol/L and 60-210 nmol/L, respectively."

Rajan S, Wallace JI, Brodkin KI, Beresford SA, Allen RH, Stabler SP. Response of elevated methylmalonic acid to three dose levels of oral cobalamin in older adults. J Am Geriatr Soc. 2002;50:1789-1795.

"Normal ranges for the serum metabolites (calculated as the mean +/- 2 SD after log transformation to correct for skewness of data towards higher values) are MMA, 73 to 271 nmol/L;"

Robertson J, Iemolo F, Stabler SP, Allen RH, Spence JD. Vitamin B12, homocysteine and carotid plaque in the era of folic acid fortification of enriched cereal grain products. CMAJ. 2005;172:1569-1573.

"We defined vitamin B12 deficiency as a serum vitamin B12 level of less than 258 pmol/L with homocysteine levels of 14 µmol/L or more or methylmalonic acid levels of 271 nmol/L or more.11"

Ruscin JM, Page RLn, Valuck RJ. Vitamin B(12) deficiency associated with histamine(2)-receptor antagonists and a proton-pump inhibitor. Ann Pharmacother. 2002;36:812-816.

"Reference range 53-271 nmol/L. {for MMA}"

Solomon LR. Cobalamin-responsive disorders in the ambulatory care setting: unreliability of cobalamin, methylmalonic acid, and homocysteine testing. Blood. 2005;105:978-985.

"MMA levels below 251 nmol/L and those reported as below 400 nmol/L were considered to be normal, while values of 251 to 376 nmol/L were considered to be moderately increased (ie, 2 to 3 SD above the normal mean) and values above 376 nmol/L were considered to be elevated (ie, more than 3 SD above the normal mean)."

Wolters M, Hickstein M, Flintermann A, Tewes U, Hahn A. Cognitive performance in relation to vitamin status in healthy elderly German women-the effect of 6-month multivitamin supplementation. Prev Med. 2005;41:253-259.

"23 (10.6%) women had MMA values exceeding the desirable cutoff of 271 nmol/L [35,54]."

Yazdanpanah M, Chan PC, Evrovski J, Romaschin A, Cole DE. An improved assay for plasma methylmalonic acid using chemical ionization gas chromatography mass spectrometry. Clin Biochem. 2003;36:617-620.

"A set of EDTA-anticoagulated samples were obtained from 108 adults recruited at an ambulatory care clinic [61 females, 47 males, age 43 +/- 13 years (mean +/- SD)] and analyzed to generate a reference interval (2.5th to 97.5th centile) of 75 to 378 nmol/L, and a median of 155 nmol/L."