Abstract

Vitamin B12 deficiency is believed to affect around 20% of seniors. As this condition can cause memory impairment and even dementia, which becomes irreversible if not treated quickly, diagnosing and treating suspected B12 deficiency quickly and accurately is very important. Unfortunately, the usual B12 blood level test can sometimes be inaccurate, and thus a more reliable test, methylmalonic acid, is often requested to diagnose B12 deficiency.

Over a number of years, it was observed that tests for methylmalonic acid that were requested for seniors both at Ste. Anne's 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 methylmalonic acid determinations, with the reference range usually used in research, it became clear that there was a large discrepancy. When this was corrected, methylmalonic acid tests finally became useful, not only to Ste. Anne clinicians, but to all the McGill and University of Montreal affiliated hospitals as well.

Résumé

On croît qu'environ 20 p. cent des personnes âgées sont atteintes d'une carence en vitamine B12. Parce que cette condition peut entraîner des pertes de mémoire et même des démences qui deviennent irréversibles lorsqu'il y a un délai de traitement, il est très important de diagnostiquer et de traiter rapidement des carences soupçonnées en vitamine B12. Malheureusement, le test le plus couramment utilisé pour déterminer le niveau de B12 dans le sang est parfois imprécis; un test plus fiable, l'acide méthylmalonique, est souvent nécessaire afin de diagnostiquer une carence en B12.

Pendant un certain nombre d'années, il a été observé que les résultats obtenus pour les tests d'acide méthylmalonique requis pour les personnes âgées à l'Hôpital Sainte-Anne, et précédemment à l'Hôpital général juif, ont toujours été lus comme normaux, même pour les patients chez lesquels des carences claires en B12 avaient été détectées par d'autres moyens. Même d'un point de vue statistique, il aurait été attendu qu'au moins 20 p. cent soient anormaux.

En comparant l'étendue de référence de la gamme de normales du laboratoire où nos analyses d'acide méthylmalonique sont effectuées avec l'étendue de référence habituellement utilisée en recherche, un écart important a clairement été constaté. Quand cet écart a été corrigé, les tests d'acide méthylmalonique se sont finalement avérés fort utiles, non seulement pour les cliniciens de l'Hôpital Sainte-Anne, mais également pour tous les hôpitaux affiliés à l'Université McGill et à l'Université de Montréal.

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

Methods

- 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 does 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 GiDossier status. 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)

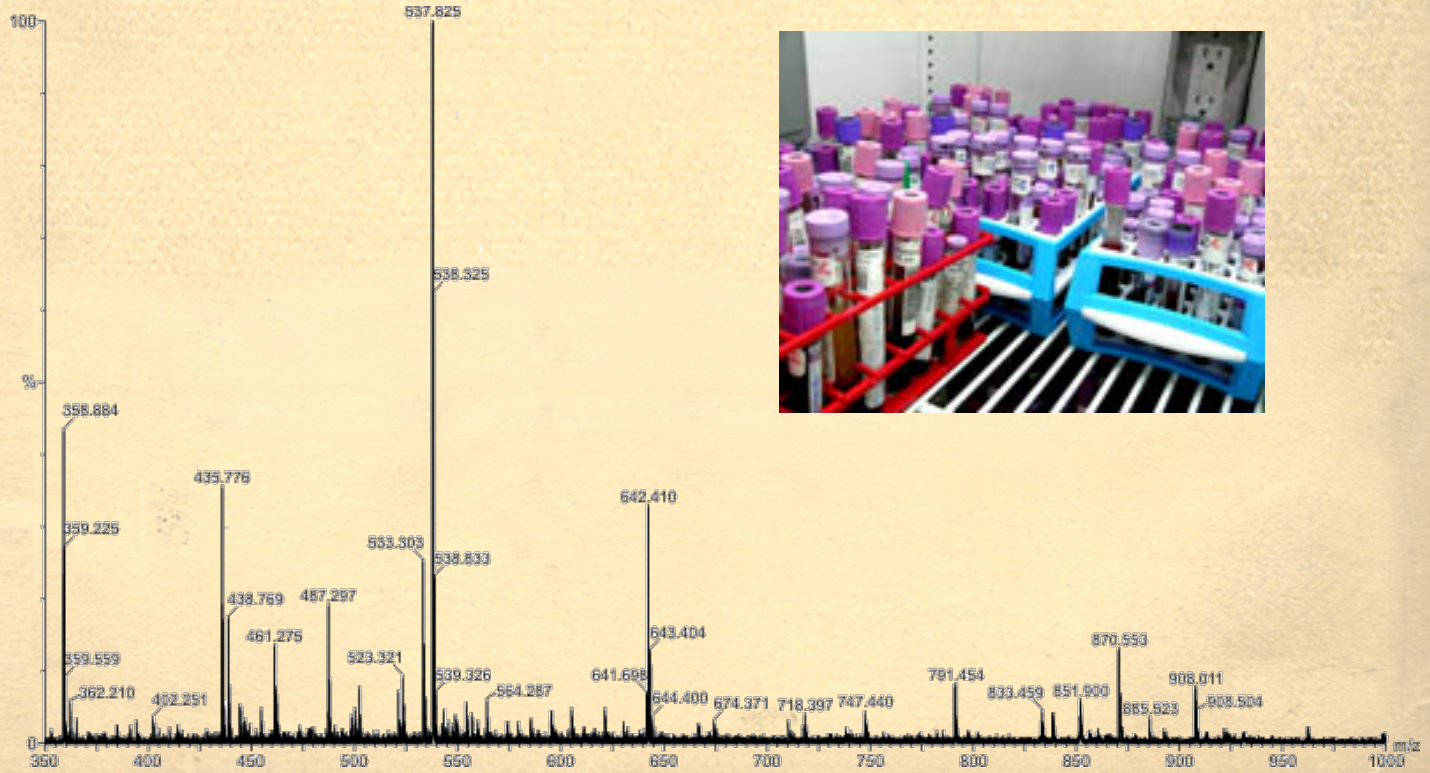
Results

- Using PubMed, 16 recent articles were found which stated reference range values for MMA testing (http://henry.olders.ca/wiki/index.php?title=Reference_range_for_Methylmalonic_Acid).
- 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

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 is now being 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.
- Dr. Mamer and I are planning to explore the connection between MMA test results and mortality for patients in McGill hospitals.

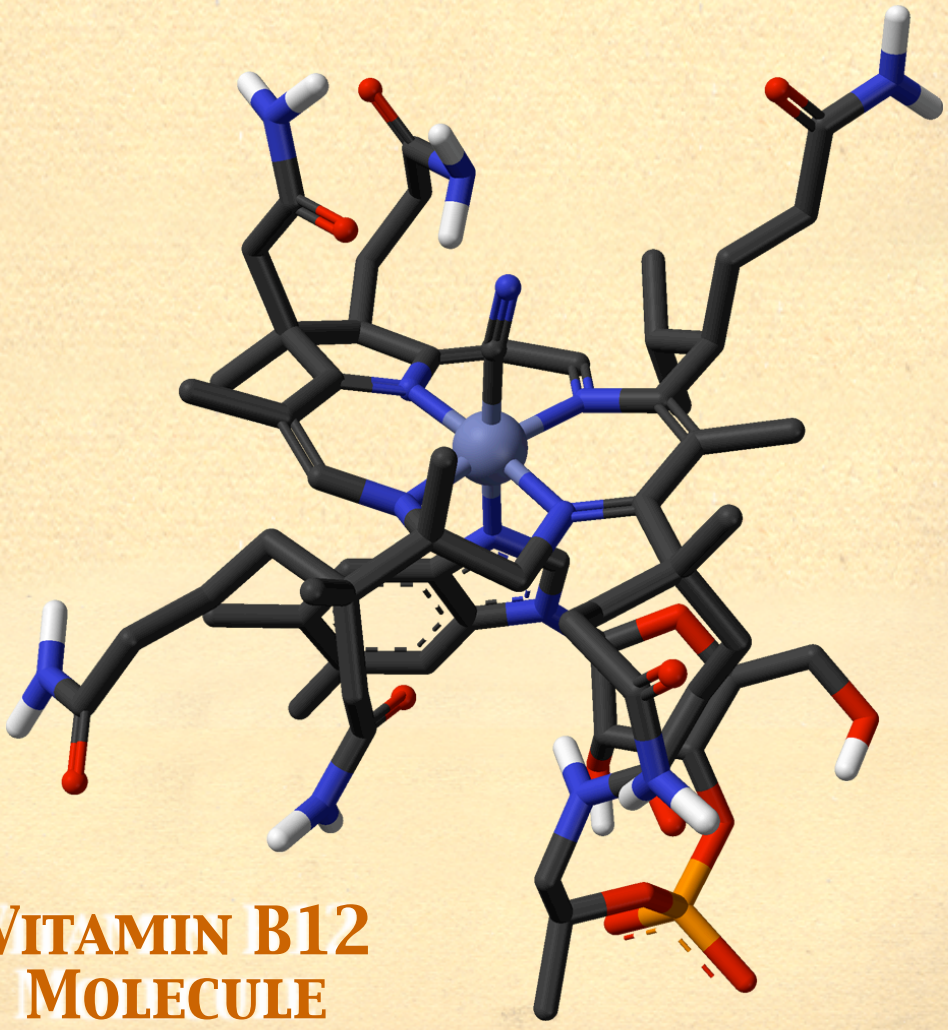


Conclusions

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

Methylmalonic acid testing with the appropriate reference range detects abnormalities in about half of patients suspected of having a B12 deficiency.

An abnormal MMA result appears to predict increased mortality.



Vitamin B12 Molecule