To the editor:

Cobalamin-responsive disorders and unreliability of cobalamin, methylmalonic acid, and homocysteine testing

Solomon[1] claims that many patients with clinical features suggestive of cobalamin (Cbl) deficiency who have normal serum Cbl, methylmalonic acid (MMA), and homocysteine (HCys) levels may respond to Cbl therapy, while many patients with low serum Cbl, high serum MMA, or high serum HCys levels may fail to respond to Cbl therapy. He concludes that these tests are unreliable for the diagnosis of Cbl deficiency. I do not think that there is much support for his conclusion.

First of all, Solomon writes that resolution of signs and symptoms consistent with Cbl deficiency in 12 patients occurred prior to any Cbl therapy. How can he then attribute to Cbl therapy the resolution of signs and symptoms of those who received Cbl?

Second, the response to pharmacologic doses of Cbl does not support the diagnosis of Cbl deficiency. The dose of Cbl for a therapeutic trial of Cbl deficiency is 1 μg Cbl daily for 10 days. This dose would produce optimal reticulocyte response within 7 to 10 days and, if continued, would produce a complete hematologic response.[2] Patients who do not respond to small doses of Cbl but respond to pharmacologic doses of Cbl are not Cbl deficient.

Third, the criteria that Solomon has used for demonstrating a response to Cbl therapy (5 fL reduction of mean corpuscular volume [MCV] or an increase in hematocrit of 0.05 point within 3 months of Cbl therapy) are nonspecific. Such a response can be seen in a patient who has folate-deficiency anemia treated with high doses of Cbl.[2] Similar hematologic changes may be seen in any patient with alcoholic liver disease or ethanol abuse who stops drinking ethanol; in patients recovering from acute hemolytic anemia, anemia associated with acute infection; or in patients with hypothyroidism treated with thyroid extract, irrespective of whether they are given Cbl.

Fourth, of 8 patients who met Solomon's criteria for hematologic response, only 2 demonstrated an increase in hematocrit within 3 months of Cbl therapy. The other 6 patients showed only reduction of MCV. If the reduction of MCV were due to Cbl therapy, why did the hematocrit not increase?

Finally, Solomon reports that low or intermediate Cbl levels were present in 46% of the responders and 56% of the nonresponders, and increased MMA values were present in 73% of responders and 88% of nonresponders. Consequently, he claims that these tests are unreliable. In the presence of low serum Cbl or high serum MMA, failure of response to Cbl does not exclude Cbl deficiency, but indicates that the anemia or neurologic abnormalities were not due to Cbl deficiency.

Serum Cbl, MMA, and HCys, like any other laboratory tests, may give false-positive or false-negative results in certain situations. One has to be familiar with these situations in order to interpret the laboratory results properly rather than claiming that these tests are unreliable.

A. Majid Shojania

Correspondence: A. Majid Shojania, St Boniface General Hospital, Winnipeg, MB, Canada, R2H 2A6; e-mail: shojana@cc.umanitoba.ca.

References

1. Solomon LR. Cobalamin-responsive disorders in the ambulatory care setting: unreliability of cobalamin, methylmalonic acid, and homocysteine testing. Blood. 2005;105:978-985.
2. Herbert V. Megaloblastic anemia. N Engl J Med. 1963;268:368-371.

To the editor:

Is testing for clinical cobalamin deficiency truly unreliable?

Cobalamin and metabolite assays' sensitivities depend greatly on whether the tested patients have clinical abnormalities (95%-99% sensitivities) or not (< 70% for cobalamin, but data and criteria vary).[1,2] In his report of massive diagnostic failures in even symptomatic cobalamin deficiency, Solomon misperceives what failed.[3]

The likeliest initial culprit is a defective cobalamin assay. Overlapping the study's time period, we reported that the ADVIA Centaur (Bayer Diagnostics, Tarrytown, NY) assay produced falsely normal results in 16 of 22 cobalamin-deficient sera that had consistently subnormal levels by 2 radioisotopic assays.[4] Assay error best explains Solomon's truly unprecedented claims that just 5 (14%!) of 37 patients with symptomatic deficiency had cobalamin levels less than 200 ng/L or that as many as 20 (54%) of 37 could have had levels more than 300 ng/L.

As to metabolite data, the pretreatment values were very inconsistent and frequently jumped the divide between normal and abnormal. Left unexamined were whether assay or patient fluctuation was responsible and if variability rather than therapy explained the (unreplicated) posttreatment improvements. Equally puzzling was the tendency of results to be less, not more, abnormal in presumably deficient patients than in nondeficient ones.

The clinical and therapeutic diagnoses raise concerns too. Hematologic findings, which lacked individual complete blood count (CBC) details, were surprisingly insubstantial. Only 2 of 37 patients had anemia, 1 of whom incongruously "responded" to cobalamin without changing mean corpuscular volume; 6 others (75% of hematologically abnormal patients) had mild macrocytosis without anemia, something that more often reflects alcoholism,[5] which, being often both unrecognized and fluctuating, can confound therapeutic assessments; and blood smears were not examined for hypersegmentation, a major failing given the study's goals and controversial findings. Neurologic information was sketchy, and the appendices suggest diagnostic alternatives; patient 3, for example, closely mimics a reported patient whose alcohol-induced neurologic and other abnormalities were mistakenly deemed