How B12 Deficiency Can Impact on the Individual and How Society can Impact on B12 Deficiency

Yuval Gielchinsky MD, Deborah Elstein PhD, Ayala Abrahamov MD and Ari Zimran MD

Gaucher Clinic, Shaare Zedek Medical Center; Jerusalem, Israel

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Textbook knowledge is invaluable to both veteran and novice clinicians in that it provides the bedrock of common wisdom upon which one builds the edifice we call differential diagnosis. This commonalty of experience is further reinforced in grand rounds and ward rounds, and is also supported by adjunct procedures and laboratory tests that become inseparable from the diagnosis itself. Thus, in the case of the clinical diagnosis of vitamin B12 deficiency, which, like folate deficiency does not initially manifest itself clinically as a full-blown syndrome, the differential diagnosis is largely based on an abnormal laboratory finding – macrocytic anemia. Macrocytic anemia, by virtue of decades-long experience, is known to be part and parcel of the deficiency state, yet recognition of the anemia as macrocytic is actually not the first stage clinically. First is the occurrence of anemia, second is the observation that the anemia is macrocytic; and only then does the suspicion of an underlying cobalamin or folate deficiency arise [1]. Thus, it is generally accepted that once there is evidence of macrocytic anemia, B12 or folate deficiency should be suspected, and this initiates the cascade of laboratory evaluations necessary to confirm the diagnosis.

Yet, there is a greater diversity of the non-hematological clinical features that are associated with vitamin B12 deficiency, they extend across a wider range of medical specialties, and they may indeed precede evidence of macrocytic anemia. Among these features are non-specific symptoms such as fatigue (without anemia) and lack of energy; cognitive deficits such as memory loss, irritability, and mood swings; gastrointestinal complaints, including motility disorders, anorexia, flatulence, and disturbances in bowel habits; patchy hyperpigmentation; and even reproductive problems, such as infertility in either males or females [2].

Interestingly, in the case of cobalamin and folate deficiencies, it is the availability of more sophisticated and more specific methods of diagnosis that has uncovered an increasing number of patients who lack the classical textbook features but do in fact have these deficiencies. Carmel [3] noted that in 70 patients with confirmed but untreated pernicious anemia who were initially screened because of serum cobalamin levels < 200 pg/ml, anemia was absent in 19% and macrocytosis in 33%. While it may be argued that macrocytosis has been masked in some cases because of the presence of a concomitant microcytic process such as iron deficiency, or the anemia of chronic disease or thalassemia minor [4,5], it is important to stress that macrocytic anemia is not generally the presenting clinical finding. Anemia is a later stage in the sequence of metabolic events in vitamin deficiency that ultimately induce abnormal laboratory findings. Preceding this is a depletion of body stores of the vitamin, leading to reduced (but not abnormal) circulating levels, and the biological effect is manifested by increased levels of the metabolites homocysteine and methyl-malonic acid in both blood and urine [6]. Only in the final phases do tissue effects occur that induce the typical megaloblastic changes – macrocytosis and anemia.

This editorial is thus directed to practicing physicians who are not sufficiently aware of the above chain of events, partially because it is not necessarily incorporated in the treasury of textbook information, in the hope of alerting them to the penultimate subclinical stages of vitamin B12 deficiency and thereby preventing more serious clinical manifestations. Among our other objectives is to make physicians cognizant of continually decreasing laboratory parameters even when still within the normal range, and to emphasize the option of conducting an analysis of the B12 metabolites (HCY and MMA) not only in a research setting [7].

The onset of clinical and laboratory evidence of folate deficiency is more rapid than for cobalamin deficiency. This is largely due to the difference in size of the body stores and in the daily minimum requirement for each of the two vitamins. The interim between inadequate intake to development of the full-blown manifestations of folate deficiency is 4–5 months. However, no comparable trajectory can be extrapolated for cobalamin deficiency, except from observations on the development of cobalamin deficiency in patients after total gastrectomy. In such patients, complete depletion of normal body stores extends over several years; this, incidentally, explains the negligible incidence of B12 deficiency among children. On the other hand, the development of cobalamin deficiency among individuals who present with low baseline levels is apparently more accelerated.

HCY = homocysteine
MMA = methyl-malonic acid

Of interest is the recent awareness of cobalamin deficiency as part of the differential diagnosis of patients who present with predominantly or exclusively neurological manifestations [8]. Notwithstanding the controversy regarding a correlation of neurological signs with severity of anemia [9] or the lack thereof [10], Rafik Masalha and colleagues provide an illustrative example in the current issue of *IMAJ* [11]. They describe two Bedouin women who presented with acute psychosis, which was reversible, at 8 and 12 weeks respectively, following treatment with intamuscular injections of cobalamine. Both patients remained symptom free for one year or more by virtue of continued oral therapy with hydroxycobalamin 300 μg daily.

Dramatic presentations, similar to these cases, are important and educational. Not only are they a powerful reminder of potentially serious, albeit atypical, manifestations of B12 deficiency, but they also provide unequivocal evidence that such abnormalities are easily reversible via the simple and inexpensive administration of cobalamin. In neither of the cases described by Masalha et al. [11] was there macrocytic anemia: this was due to high folate levels in one patient and to low serum iron levels in the other. The fact that both patients were Bedouin raises the question whether this ethnic group in Israel is more prone to vitamin B12 deficiency than others. Although a definitive answer cannot be given to this question at present, a study recently conducted by our group revealed an unexpectedly high prevalence of low vitamin B12 levels among several ethnic groups in Israel [12]. These findings are soon to be published [12]. In that study, there was a > 30% incidence of low B12 levels in Ashkenazi healthy controls, while other ethnic groups showed a > 12% incidence of low serum B12 concentrations. This apparently high incidence among healthy blood donors was also high compared to levels found in other populations with B12 deficiency in other countries.

The questions that were raised consequent to the study in healthy Israelis were primarily based on the finding that B12 deficiency was apparently pan-ethnic in Israel, inferring that an environmental modifier may be more important than a genetic predisposition (such as an inherited deficiency in transcobalamin) in our country. Based on the cases reported by Masalha et al. [11], one may also question whether there may be an (unidentified) acquired factor that is more prevalent in the Negev, where many Bedouin live. More logical, however, would be the assumption of an environmental factor that transcends the small geographic entity of Israel, and hence may affect other peoples living in the Mediterranean Basin, suggesting a cooperative effort such as a large-scale screening of all the peoples in this area.

While the causes of B12 deficiency should be investigated and are of both academic and practical interest, dealing with the therapeutic options as well as developing a comprehensive medical policy by the Ministry of Health should not have to await the results of future studies. Given the low cost of treatment and the simple manner of testing for folate and vitamin B12 status, appropriate directives should be instituted immediately. These should include recommendations for oral or sublingual medication [13], food fortification [14], large-scale screening of the specific populations particularly the Bedouin, and distribution of guidelines for primary healthcare providers, prenatal clinics, school nurses, etc. In addition, we would also recommend adding the B12 assay to routine blood tests in various clinical settings, as well as for all patients with psychiatric disorders. Similar directives should be considered regarding the traditional attitude vis-a-vis the need to perform the Schilling test in every subject with B12 deficiency, given the large segment of our population who may be found to be affected [15]. At least among younger individuals in our cohort [12], none has been identified with pernicious anemia based on a pathological Schilling test, implying therefore that this test be performed only in those with a more specific finding.

When academicians conduct population studies, as in the above unsolicited pilot of B12 levels in healthy individuals, there is the potential that researchers' scientific aspirations to produce unbiased data may prompt commercial interest upon which the results may impact. For example, in the case of vitamin deficiency, the conclusion of a pervasive deficiency should alert our national health officers to deal with a solution that is community-based and effective, without undue influence of pharmaceutical and vested interests. The responsibilty of society is to acknowledge the ills of its citizens and provide creative solutions. What would be unacceptable in a moral society is to allow the problem to be trivialized by those elected to deal with it. Thus, it is to the long-term detriment of those health maintenance organizations that have chosen to further reduce the lower limit of normal B12 levels in their attempt to dismiss the existence of a real medical problem. In Israel this is even more unacceptable since the specific therapy for persons with B12 deficiency is both inexpensive and immediately effective. Moreover, this is in stark contrast to the policy regarding other disorders, such as the non-fatal lysosomal storage diseases, for which the health authorities readily undersign the exorbitant cost per patient (potentially more than $100,000 a year for the rest of the patient's life) and require no long-term surveillance of the drug's continued effectiveness. For individuals with a vitamin deficiency such as cobalamin or folate, our society should re-prioritize by investigating ways to provide the greatest degree of healthcare to the greatest number of its citizens.

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Correspondence: Dr. A. Zimran, Gaucher Clinic, Shaare Zedek Medical Center, P.O.Box 3235, Jerusalem 91031, Israel. Phone: (972-2) 655-5673, Fax: (972-2) 651-7979, email: zimran@md.huji.ac.il