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Diagnosis of Vitamin B12 Deficiency

Editorial

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Vitamin B12 (cobalamin) deficiency occurs primarily as a result of insufficient dietary intake or poor absorp-tion. There is widespread global prevalence of vitamin B12 deficiency, resulting in considerable morbidity [1].

Anemia is the most common presenting feature of vi-tamin B12 deficiency but it can also present with a vari-ety of neurologic and psychiatric manifestations in the absence of anemia. This list of presentations contin-ues to expand. For example, I have recently described 2 patients with long histories of drenching night sweats without any other constitutional symptoms, who had been investigated extensively over a period of several years. Both had low normal vitamin B12 levels but high homocysteine levels and had a dramatic response to vitamin B12 therapy, Objective improvement in clini-cal symptoms after the intervention proved that the diagnosis of vitamin B12 deficiency was sound even though vitamin B12 levels were in the low-normal range [2]. In addition, subclinical cobalamin deficiency without anemia or other neuropsychiatric symptoms is increasingly being recognized [3]. It is however, not known, to what extent this subclinical deficiency of vi-tamin B12 contributes to non-specific symptoms such as fatigue and tiredness.

Despite widespread prevalence of vitamin B12 deficiency, its diagnosis is fraught with problems. Vitamin B12 status can be assessed by directly measuring the vitamin in the blood or by measuring the metabo-lites that accumulate as a result of deficiency. Vitamin B12 assay is usually the first step but both false posi-tive and false negative results are common [4]. It has been shown that 10% of patients with clinical or meta-bolic evidence of vitamin B12 deficiency have plasma or serum vitamin B12 levels of 150 to 221 nmol/L [5]. In addition, there is poor correlation with differ-ent assays used to assess vitamin B12 status. Vitamin B12 is a cofactor for two enzymes: methionine syn-thase and L-methylmalonyl-coenzyme A mutase [6]. Measurement of metabolites like total homocysteine (Hcy) and/or methylmalonic acid (MMA) provides an alternative method of diagnosing vitamin B12 deficiency. Levels of both Hcy and MMA are elevated in >98% of patients with clinical vitamin B12 deficiency [7].Measurement of Hcy and MMA can also be used to monitor response to treatment since the levels of Hcy and MMA decrease immediately after treatment [8].However, elevated Hcy and MMA levels are not specific to vitamin B12 deficiency. Hcy levels are also elevated in renal failure, folate deficiency, hypothyroid-ism, and homocystinuria and other genetic disorders while MMA levels are elevated in renal failure. Many drugs also affect plasma Hcy levels. Estrogens, tamox-ifen and statins decrease while L-dopa, fibrates and diuretics increase Hcy levels[9].

More recently, assays have been developed to measure the transcobalamin fraction of vitamin B12 (holo-TC).Studies have shown that sensitivity and specificity of holo-TC is about equivalent to total serum vitamin B12 and measurement of holo-TC in conjunction with vitamin B12 improves the predictive value for identify-ing vitamin B12 deficiency [10]. These assays are, however, not yet widely available.

The National Health and Nutrition Evaluation Sur-vey (NHANES) recommend using at least two mark-ers and diagnosing vitamin B12 deficiency when both are abnormal [11]. It recommends measuring at least one biomarker of circulating concentrations of vita-min B12 (vitamin B12 or holo-TC) and one biomarker of functional vitamin B12 status (MMA or Hcy). The panel advised that vitamin B12 deficiency should be diagnosed only when both markers are abnormal. This approach however, will result in under-diagnosis of vitamin B12 deficiency. Since vitamin B12 deficiency can have non-specific symptoms like malaise, fatigue and ill-defined cognitive impairment and since new manifestations of vitamin B12 deficiency are becom-ing obvious, untreated deficiency can result in serious morbidity and even permanent neurological damage. It would therefore, be prudent to treat empirically all those with a single abnormal result and suggestive clin-ical findings. This approach will obviously need careful clinical monitoring to make sure that the health out-come of such an intervention is positive and to reas-sess the management strategyy if it is not.

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