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LETTER TO THE EDITOR

Low Serum Vit. B12 Level Does Not Mean Vit. B12 Deficiency – Problems Related to the Diagnosis of Vitamin B12 Deficiency

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I have read with an interesting paper by Türkyılmaz et al., in which they described the temporal quadrant RNFL thickening in patients with Vitamin (vit.) B12 deficiency.[1] However, the diagnosing of vit. B12 deficiency raises some questions, and thus it needs some further discussion.

THE IMPORTANCE OF THE CLINICAL PICTURE OF THE VIT. B12 DEFICIENCY

The clinical picture of vit. B12 deficiency might be highly polymorphic and of varying severity, ranging from more common conditions, including sensory neuropathy and isolated anomalies of macrocytosis and hypersegmentation of neutrophils, to rare and severe disorders. Neurological symptoms without anemia were reported in 20%–30% of vit. B12 deficiency cases,[2] however, neutrophil hypersegmentation and macro-ovalocytosis are present on the blood films of most patients with megaloblastic hemopoiesis.[3] On the other hand, it is known that low serum vit. B12 level is not automatically diagnostic for vit. B12 deficiency in asymptomatic, hematologically normal patients.[4] Thus, the clinical picture is crucial for determination of the vit. B12 deficiency. The studied group in the discussed paper consisted of 45 patients with vit. B12 level lower than 189 pg/mL, including 37 asymptomatic patients and eight with peripheral neuropathies.[1] Unfortunately, no information of their blood film abnormalities was provided.

SUBCLINICAL COBALAMIN DEFICIENCY

It was shown in many studies that some patients with low cobalamin levels (<200 ng/L) lacked clinical evidence of deficiency. Thus, it was argued that a low serum cobalamin (<200–250 ng/L) cannot be taken automatically as diagnostic for cobalamin deficiency in asymptomatic, hematologically normal patients. It was shown that serum cobalamin levels less than 200 ng/L (148 pmol/L), or less than 250 ng/L with some assays, are common, especially among the elderly,[5] and approximately 22%–30% of them are falsely low by both metabolic and clinical criteria[6,7] and most of the rest are clinically innocent.[4,5]

It is well-known that methylmalonic acid (MMA) and homocysteine (HC) increase in vit. B12 deficiency.[8] It was postulated that deficiency diagnosis should be based on at least two unrelated biochemical abnormalities (e.g. cobalamin and MMA) because an isolated biochemical abnormality (e.g. MMA alone) may also be spurious, unless confirmed by its normalization with cobalamin therapy.[4]

The different strategies to deal with these problems were proposed. Just to mention some of them, Hvas & Nexo suggested the use of the reference interval (156–672 pmol/L) for vit. B12, including B12 deficiency when <125 pmol/L, gray area when 125–250 pmol/L and not B12 deficient when >250 pmol/L.[3] Carmel also proposed that low-normal vit. B12 level (250–350 ng/L) need not be tracked if accompanied by no

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clinical evidence of deficiency.[4] Thus, the important task is to document the clinical and laboratory findings and prove their connection to cobalamin deficiency, what was not presented in the discussed study.

PATHOPHYSIOLOGY OF VIT. B12

The next important issue, not addressed at all in the analyzed paper, is the cause of the vit. B12 deficiency. The pathophysiology of cobalamin is different from most other vitamins, such as folate, that the daily requirement is so small relative to stores that deficiency typically takes years to develop in adults and only infrequently reaches the depletion point necessary for clinical consequences.[4] It is known that 94% of patients with clinically expressed vit. B12 deficiency had IF-related malabsorption, such as pernicious anemia or sprue.[4] The reason for vit. B12 deficiency in patients in the discussed article was not given and IF-related malabsorption was not verified.

PROBLEMS WITH RELIABILITY OF VIT. B12 DIAGNOSTIC TESTS

To make the problem even more complicated it was shown in many studies that current vit. B12 diagnostic tests are unreliable.[9–12] Hamilton et al. postulated that laboratories should not report the vit. B12 level without providing the level of antibodies against the intrinsic factor, and other hematological data essential for the reliability of the diagnosis.[12] The recent reports of Yang & Cook confirm the existence of essential discrepancies in determining the vit. B12 level depending on the applied laboratory technique.[13] The problem also lies in large variation between the standards for vit. B12 depending on the manufacturer of the test. In some cases, two different studies of serum from the same patient using two tests from different manufacturers present different results from average to below average.[12] Therefore, it seems important to recognize the type and reliability of the test used in measuring vit. B12 level and consider – at least in diagnostically questionable cases – carrying out vit. B12 measurements along with the measurements of the level of antibodies against the intrinsic factor, as it was not done in the discussed paper.

DECLARATION OF INTEREST

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the article.

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