CORRESPONDENCE

Causes and Early Diagnosis of Vitamin B12 Deficiency

by Prof. Dr. med. habil. Dr. rer. nat. Wolfgang Herrmann,
Dr. rer. med. Rima Obeid in volume 40/2008

Gastrin Levels in Pernicious Anemia

Chronic atrophic gastritis can result not only in vitamin B_{12} deficiency in spite of a normal serum concentration but it can also result in a raised gastrin level, which in rare cases can rise to above 1000 pg/ml (1, 2). Since such gastrin measurements are strong indicators of a gastrin producing tumor, for example, a gastrinoma, some patients without a history of ulcers or signs of a multiple endocrine dysplasia type 1 (MEN-1) disorder are subjected to comprehensive diagnostic tests for clarification (presumed diagnosis: gastrinoma?). This may be the case especially if a gastrin concentration of more than 1000 pg/ml is associated with diarrhea, which is observed in the context of autoimmune disorders. On the other hand, atrophic gastritis and pernicious anemia in patients with polyglandular syndrome of type 1 are mostly accompanied by low/normal gastrin levels, probably because of the loss of gastrin producing cells.

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Parenteral Substitution

In vitamin B_{12} deficiency, clinical deficiency symptoms occur only when the body's own reserves of 5 mg—which are primarily stored in the liver as hydroxycobalamin—are reduced to 5–10%. Treatment has to fully restore the original level. Unfortunately, however, in most German language and English language textbooks, the recommended doses of vitamin B_{12} are too low.

In disorders where the absorption of B_{12} in the gastrointestinal tract is irreversibly destroyed—for example, in chronic atrophic gastritis of the pernicious type, after gastrectomy, or after resection of the terminal ileum—parenteral substitution is necessary (1). In choosing the appropriate available medication it is important to know that cyanocobalamin is not stored in the body to the same degree as the physiological storage depot form hydroxycobalamin (2). In my opinion, hydroxycobalamin should be the preferred option. Once B_{12} body stores are exhausted, the deficient stores need to be completely replenished as soon as possible, to prevent deficiency symptoms. On the basis of pharmacokinetic findings (2) we have achieved good results with the following pragmatic approach: 500 µg hydroxycobalamin are given intramuscularly (of which 226 µg are retained at a retention rate of 45%—the retention rate for cyanocobalamin is only 16%) on 5 days of the week for 4 weeks (22 injections in total). This completely restores the body's deposits. To balance the daily consumption of about 2.5 µg, lifelong maintenance therapy is required, with intramuscular injections every 3 months (4 times a year).

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Risk Group includes infants

The authors say that even persons with vitamin B_{12} concentrations in the reference range may show signs of vitamin B_{12} deficiency. They recommend measuring biomarkers (serum holotranscobalamin, plasma methyl malonic acid, and plasma homocystein). Measuring MMA in spontaneous urine provides a reliable, simple, and cost effective alternative (1, 2). This can be done by using gas chromatography with subsequent mass spectrometry (GC-MS). In the medical fee schedule, number 3783, "organic acids profile" is rated at 570 points (= ca. 33.22 euros). Measuring MMA in urine as a "screening method" would shorten and simplify the flow chart suggested by the authors to diagnose vitamin B_{12} deficiency (figure 2).

The authors' listed risk group for deficiency includes pregnant and breast feeding women. However, it is important to also include infants, in whom prenatal and postnatal vitamin B_{12} deficiency can cause severe and partly irreversible neurological damage. We recently reported the case of 4 infants, in 2 of whom vitamin B_{12} deficiency was caused by the mother's unidentified

pernicious anemia and in the other 2 by the mother's vegan diet. None of the mothers had clinical symptoms; severe developmental disorders in the babies, however, triggered diagnostic investigation, and raised excretion of MMA in the urine pointed the way. All babies showed neurological symptoms in later examinations (3). With regard to the severe pathology and the associated costs it is worth considering whether examination for vitamin B_{12} deficiency by measuring MMA in the urine by using GC-MS should be offered to all pregnant women.

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In Reply:

Koch reported normal serum concentrations of vitamin B_{12} and raised gastrin levels in atrophic gastritis in spite of vitamin B_{12} deficiency. We can confirm that a false positive B_{12} concentration is often observed since the diagnostic sensitivity of B_{12} measurements is relatively low. The proportion of metabolically active holotranscobalamin (holo-TC) in total B_{12} is 10–30%. A normal total B_{12} measurement in spite of a deficiency in metabolically active holo-TC can thus be explained. Measuring holo-TC is diagnostically more sensitive; additionally measuring MMA provides clues about whether the deficiency already affects the patient's metabolism—that is, whether the homocystein-methionin cycle is disrupted. In our own studies we showed that the relation between total B_{12} values and holo-TC values is not linear, but that in B_{12} serum levels below 300 pmol/l the percentage share of holo-TC in total B_{12} clearly drops, so that especially in the diagnostically interesting range of possible B_{12} deficiency the examination of total B_{12} fails and the B_{12} status therefore appears normal.

In the blood, vitamin B_{12} is present mainly as holohaptocorrin and 10–30% as metabolically active holo-TC, which is absorbed into the cells via ubiquitous transcobalamin receptors. Intracellularly, hydroxycobalamin bound to transcobalamin is separated; it is transformed into methylcobalamin or adenosylcobalamin and functions as an enzyme cofactor (methionin synthase and methylmalonyl-CoA mutase) or is stored as such. The statement that the recommended dosages of B_{12} are too low is correct. Since vitamin B_{12} is non-toxic and surplus amounts are excreted, high B_{12} dosages are unproblematic. However, only limited amounts of the B_{12} ingested in food reach the blood circulation via the receptor pathway. Additionally, a smaller proportion (3%) is absorbed via passive diffusion, independent of the receptors.

This means that high oral doses of vitamin B_{12} can result in sufficient amounts of B_{12} being absorbed into the blood stream via diffusion. Particularly elderly people often have vitamin B_{12} deficiency because of malabsorption. Daily oral administration of 0.5–1 mg vitamin B_{12} often result in metabolic normalization, without having to use parenteral B_{12} injections (1, 2). Regular laboratory controls using the modern markers of B_{12} status (holo-TC and MMA) is required.

Examining MMA in urine is without doubt an alternative method for confirming functional vitamin B_{12} deficiency. In principle, however, measuring MMA in urine is no different to measuring plasma concentrations (gas chromatography/mass spectrometry). On the contrary, the diagnostic specificity and sensitivity is higher in plasma measurements than in urine measurements, especially because the decision thresholds are much more clearly defined and international agreement has been reached (3, 4). Our diagnostic scheme cannot be shortened by measuring MMA in urine. Holo-TC as the parameter of choice captures manifest vitamin B_{12} deficiency, but also the stage of store depletion, where the B_{12} balance is negative but no functional deficit has yet developed. MMA is raised only once the reserves have been depleted, once the vitamin B_{12} deficiency has metabolic sequelae. Measuring MMA has diagnostic limitations because it is also raised in impaired renal function, among others. As far as MMA screening in urine is concerned, we wish to point out that this is expensive and available in only few centers. Holo-TC measurements can be conducted anywhere as an automated and standardized test.

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