

Hypervitaminemia B12: A Useful Additional Biomarker for the Diagnosis and Monitoring of Liver Diseases

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Abstract

B₁₂ hypervitaminemia is a biological abnormality, yet one that is significantly underestimated. According to the literature, high levels of vitamin B₁₂ is associated or linked with a range of conditions, the majority of which are serious. These conditions include solid neoplasia (whether metastatic or otherwise) and, either acute or chronic, malignant haematological disorders. But there are others causes like liver disorders, which are described in the literature, but poorly known.

Keywords: Hypervitaminemia B₁₂; Liver disorders; Hepatocellular carcinoma

Introduction

High serum levels of vitamin B₁₂ or cobalamin, also called B₁₂ hypervitaminemia, is a biological abnormality, yet one that is significantly underestimated. To date, no consensus on the management of this anomaly exists. According to the literature, high levels of vitamin B₁₂ is associated or linked with a range of conditions, the majority of which are serious, with a systematic inquiry being decisive for prognosis following the discovery of high serum cobalamin level [1]. These conditions include solid neoplasia (whether metastatic or otherwise) and, either acute or chronic, malignant haematological disorders. But there are others causes like liver disorders, which are described in the literature, but poorly known. We illustrate this problematic in this clinical case.

Case Report

We received a 57-year old patient in our unit to treat a right cardiac decompensation. This is a patient with a medical history of chronic alcoholism complicated pathology of cirrhosis classified as Child Pugh C9, a non-anticoagulated atrial fibrillation, an alcoholic polyneuropathy, and benign prostatic hyperplasia. Clinically, the patient has NYHA class 2 dyspnea with the presence of peripheral edema of the lower limbs pitting. Pulmonary auscultation found crackles in the base of the lungs without any sign of respiratory severity; this leads to the initiation of hydro-sodium depletion. On the digestive side, the abdomen is bloated, without signs of venous collateral circulation, without any transit disorders; the hernial orifices are clear. We do not notice dullness, but there is a presence of conjunctival jaundice. Liver enlargement due to cirrhosis is hardly noticeable due to a bloated abdomen. The patient does not exhibit signs of encephalopathy, or flapping tremor. We have requested an abdominal ultrasound to look for eventual ascites, which may indicate

edema-ascites decompensation. The hydro-sodium depletion enabled a regression of vascular overload signs.

The ultrasound confirms the presence of a dysmorphic liver. But this is associated to the presence of a nodule that is 2.7 cm in diameter in the right liver. It also reveals portal hypertension with inversion of the flux port. There were no ascites discovered and hepatic veins are permeable. On the biological side, a macrocytosis (MCV: 105 fl) without anemia is noted; prothrombin time is reduced to 50%. Liver function tests only show a rise in total bilirubin to be 53 µmol/l (normal laboratory value: 2-18) without liver enzymes and without cholestasis. The albumin levels are 20.5 g/l (normal laboratory value: 35-52). Note the presence of hypervitaminemia B₁₂, with an estimated rate of 865 pg/ml (normal laboratory value: 191-485 pg/ml). The ACE rate is negative and we noted an increase in the rate of alpha-fetoprotein to 200 ng/ml (normal laboratory value: <10 ng/ml)

As a result of this clinicobiological combination of the discovery of a liver nodule, high alpha-fetoprotein levels, and elevated serum vitamin B₁₂ levels, there is suspicion of hepatic neoplasia. Thus, the liver MRI performed uncovered a 25 mm nodule in the lateral right sector of the liver, which is very likely pointing towards hepatocellular carcinoma. The thoraco-abdominopelvic CT scan confirms the hyperarterialized lesion of 25 mm with wash out on the right section on a dysmorphic liver suggesting hepatocellular carcinoma. A gastroenterological treatment is prepared.

Discussion

The link between B₁₂ hypervitaminemia and solid neoplasia was demonstrated by Carmel et al. [2], when they studied vitamin B₁₂ levels and vitamin B₁₂ transporters in a population of 139 oncology patients [2]. The major cancers that were implicated were hepatocellular carcinoma (HCC) and secondary hepatic tumors, breast cancer, colon cancer, stomach cancer and pancreatic tumors [3]. Deneuille et al. [4] further defined the link between high serum levels of vitamin B₁₂ and neoplasia with an OR of 1.8 across all cancers, 2.9 for metastatic tumors, 3.3 for HCC, 4.7 for other primitive hepatic

tumors and 6.2 for neoplasia with hepatic metastasis. Fifty percent of hepatocellular carcinoma cases were linked to B12 hypervitaminemia, demonstrating a correlation with tumor size in certain cases [5]. The literature features reports of a link between B12 hypervitaminemia and acute or chronic liver disease [5]. These situations should be distinguished between acute liver disease, chronic liver disease, and hepatocellular carcinoma. In cases of acute liver disease, B12 hypervitaminemia is encountered in 25 to 40% of patients. Alcohol consumption may also be associated with elevated vitamin B12 levels, even in the absence of a manifest hepatic condition [1]. In the case of alcohol-induced hepatitis, a correlation has been reported between vitamin B12 levels of >800 pg/ml in serum and both the severity of the liver disease and the mortality rate [6]. Dou et al. [7] identify vitamin B12 as a predictive factor for severity and mortality at three months in acute cases of chronic liver disease, particularly for levels >1,200 pg/ml or even 2,000 pg/ml. Multiple studies confirm the significant link between B12 hypervitaminemia and liver disease. In an internal medicine study, 31% of patients with elevated B12 had non-neoplastic liver disease, with 80% of cases being chronic and 25% having reached the stage of cirrhosis [8]. Similarly, the BDOSE study found that alcoholism (with or without manifest hepatic abnormalities) and neoplasia was the most frequent causes of B12 hypervitaminemia [8]. Deneuve et al. [4] identified a link with an odds ratio of 4.3. Zulfiqar et al. [9] confirmed this fact, factors with a significant link to hypervitaminemia B12 in univariate analysis were: acute renal failure ($p=0.0002$); liver diseases ($p<0.0001$) and solid neoplasia ($p=0.0030$). Hepatic metastases were on the threshold of significance ($p=0.0622$), and variables independently related to hypervitaminemia B12 were: acute renal failure: (Odds Ratio [OR]=6.3; 95% CI=2.7-8.1; $p<0.0001$); liver diseases (OR=5.4; 95% CI=3.1-6.9; $p<0.0001$); hematological disorders (OR=5.7; $p=0.0017$); and age ≥ 75 years (OR=3.7; 95% CI=1.9-4.8; $p=0.0416$). The pathophysiologic mechanism is an excess cobalamin release by the liver and the hepatic synthesis decrease of Transcobalamin II, which is essential for tissue fixation of B12 vitamin [10].

Conclusion

Hypervitaminemia B12 can be used as a useful biomarker in the diagnosis of malignant liver disease, and their prognosis.

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