Does an Elevated Serum Vitamin B_{12} Level Mask Actual Vitamin B_{12} Deficiency in Myeloproliferative Disorders?

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Abstract

Elevation of the methylmalonic acid level is a sensitive marker of vitamin B_{12} deficiency. Our cross-sectional observational study of 33 patients with myeloproliferative disorders found that 9 patients, 27.27% had occult deficiency despite having normal to elevated serum vitamin B_{12} levels. Early detection of vitamin B_{12} deficiency by using the methylmalonic acid measurement may prevent significant neurologic and hematologic complications in patients with myeloproliferative disorders.

In patients with myeloproliferative disorders, normal to high serum vitamin B_{12} concentrations have often been reported. The primary objective of this study was to determine whether normal or elevated serum vitamin B_{12} levels in myeloproliferative disorders might actually mask the true underlying vitamin B_{12} deficiency in some patients. Thirty-three patients (12 men, 21 women; mean age, 70.55 years [range, 37-90 years]) with polycythemia vera (n = 13), essential thrombocythemia (n = 12), chronic myelogenous leukemia (n = 5), and idiopathic myelofibrosis (IMF) (n = 3) were accrued over a period of 1 year, from March 2009 to February 2010. From all of the subjects, serum vitamin B_{12} level, methylmalonic acid level, a basic complete blood cell count panel, and liver and renal function tests were obtained. Normal to elevated serum vitamin B_{12} levels were recorded in all the patients. However, elevated serum methylmalonic acid levels were found in 9 (27.27%) patients, with a prevalence of 2 patients with polycythemia vera, 23% in polycythemia vera, 4 patients with essential thrombocythemia, 33.3% in essential thrombocythemia, 1 patient with chronic myelogenous leukemia, 20% in chronic myelogenous leukemia, and 2 patients with idiopathic myelofibrosis, 66.7% in IMF. Our data suggest that 27.27% of the total enrolled patients had occult vitamin B_{12} deficiency despite normal to elevated vitamin B_{12} levels on regular serum vitamin B_{12} testing.

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Introduction

Myeloproliferative disorders (MPD) is a term first coined by William Dameshek in 1951 to describe a heterogenous group of diseases with subtle clinical and biochemical features.[1] These include polycythemia vera (PV), essential thrombocythemia (ET), chronic myelogenous leukemia (CML), and idiopathic myelofibrosis (IMF).[2] These MPD can further be classified as CML-MPD due to the presence of the Philadelphia chromosome and *bcr/abl* fusion protein or non-CML MPD, which have in common an acquired point mutation in the JAK2 kinase gene.[3] MPDs are characterized by effective clonal myeloproliferation without dysplasia,[4] elevated numbers of nonlymphoid cells with or without platelets in peripheral blood, and a hypercellular bone marrow, splenomegaly, constitutional symptoms, and an increased likelihood for thrombosis.[5] The rapid proliferation of cells may lead to depletion of folate and vitamin B_{12}.[6] Interestingly, high levels of serum vitamin B_{12} (also referred to as cobalamin interchangeably) have been demonstrated in patients with MPD.[7-10]

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Table 1 Laboratory Parameters of the 33 Subjects With MPD Who Were Enrolled in the Study

	CML (n = 5)		ET (n = 12)		IMF (n = 3)		PV (n = 13)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age, y	67.2	50-85	76.8	50-90	62.6	52-84	67.8	37-86
Hb, g/L	12.3	11.3-13.6	12.6	9.8-17.2	10	8.8-10.9	15	10-19.5
Hct, %	36.8	33.1-40.1	39	27.9-79.6	30	26.4-30.3	45.2	29.9-58.7
MCV, fL	90.2	86-93	104.3	85-121	98	91-105	94.3	68-132
WBC, $\times 10^8$/L	22.7	4.4-81.6	8.7	2.4-13.8	15	4.7-25	16.6	4.7-59.6
Plt, $\times 10^9$/L	268.8	226-1000	657.1	267-1703	351.7	135-574	428.3	204-1011
B_{12}, ng/L	523.6	211-1500	622	263-1275	1388.7	1003-1647	701.8	348-1679
MMA, nmol/L	269	200-338	258.9	109-438	357	180-488	251.2	141-364
LDH, IU/L	285.8	161-445	271.3	181-545	443.7	261-780	314.3	190-530
SUN, mg/dL	23.2	12-36	18.6	9-31	37.5	29-46	21.3	8-33
GFR > 60 ml/min	2	–	9	–	3	–	12	–
GFR < 60 ml/min	3	–	3	–	0	–	1	–
Elevated Cr, mg/dL	2	–	2	–	0	–	4	–
Normal Cr, mg/dL	3	–	10	–	3	–	9	–
AST, U/L	22.2	15-38	30.8	11-61	20.3	13-28	22.8	14-31
ALT, U/L	18.4	12-30	25.8	8-61	13.7	11-20	19.8	11-36
Tot Bil, mg/dL	0.6	0.3-1	0.6	0.3-1.1	1.1	0.2-2.5	0.7	0.3-1.2

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; B_{12} = vitamin B_{12}; CML = chronic myelogenous leukemia; Cr = creatinine; ET =essential thrombocythemia; GFR = glomerular filtration rate; Hb = hemoglobin; Hct = hematocrit; IMF = idiopathic myelofibrosis; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; MMA = methylmalonic acid; MPD = myeloproliferative diseases; Plt = platelet count; PV = polycythemia vera; SUN = serum urea nitrogen; Tot Bil = total bilirubin; WBC = white blood cell.

Vitamin B_{12} is a micronutrient that plays a vital role in a myriad of biologic functions, including 1-carbon metabolism,[7] DNA and neurotransmitter synthesis, myelin sheath homeostasis, and erythropoiesis.[11,12] In serum, vitamin B_{12} is bound to haptocorrin (HC) and transcobalamin II (TCII).[7] HC is mainly synthesized in cells of the myeloid lineage and is involved in binding 80%-94% of endogenous plasma vitamin B_{12}. It may have a role in binding harmful vitamin B_{12} analogues and direct them to the liver for secretion in bile. By contrast, TCII is synthesized in enterocytes and is essential for the uptake of 6%-20% of the endogenous vitamin B_{12} from the ileum into the blood as well as into other cells through receptor-mediated endocytosis.[7] As a result, only vitamin B_{12} that is bound to TCII is available for cellular uptake, and, therefore, the likelihood of vitamin B_{12} deficiency increases, especially in high-risk groups such as those older than age 50 years due to malabsorption of protein-bound vitamin B_{12}, individuals with disorders of the gastrointestinal system, and those on a vegetarian diet among others.[13] Clinically, vitamin B_{12} deficiency presents with irreversible neurologic impairment; psychiatric involvement, such as dementia or depression; or hematologic impairment.[12]

Given the tendency of vitamin B_{12} deficiency and MPDs to occur in those patients older than 50 years, it is important to investigate whether these conditions are occurring concurrently. The specificity and positive predictive value for serum vitamin B_{12} level is too low to demonstrate vitamin B_{12} deficiency at the tissue level.[14,15] Another marker that has been used for vitamin B_{12} deficiency includes elevated homocysteine levels, but this is not specific to vitamin B_{12} deficiency because the pathway that requires the conversion of homocysteine to methionine also requires vitamin B6 and folate.[13] Given that vitamin B_{12} is solely required for the conversion of methylmalonic acid (MMA) to succinyl-coenzyme A (CoA), measuring the MMA level is preferred because it has been shown to be highly sensitive[16] and a functional biomarker[7] for cobalamin deficiency. Faurschou et al[6] demonstrated cobalamin deficiency in PV and IMF but did not elaborate on its significance. The objectives of this study were to determine if using MMA levels as a screening tool aids in detecting a true vitamin B_{12} deficiency and to estimate the prevalence of vitamin B_{12} in MPD.

Patients and Methods

Patients

This is a cross-sectional, observational study. The protocol was approved by the institutional review board at St Joseph's Regional Medical Center. The inclusion criteria were the diagnosis of an MPD according to the guidelines set out by the World Health Organization[6] and normal-to-high serum vitamin B_{12} levels. The exclusion criteria were patients with gastrointestinal disorders such as Crohn disease, prior gastric or ileal resection, or concurrent metformin use, or being on a purely vegetarian diet. From 33 patients with MPD, venous samples were collected into tubes that contained heparin as an anticoagulant. Among the patients, 13 had PV, 12 had ET, 5 had CML and 3 had IMF. The study comprised a total of 12 men and 21 women, with the mean age of 70 years (range, 37-90 years). Complete blood cell count, complete metabolic panel, serum vitamin B_{12} level, and MMA levels were measured in all cases.