Prevalence of Vitamin B_{12} Deficiency Among Geriatric Outpatients

Yulin Yao, MD; Siu-Long Yao, MD; Siu-Sun Yao, MD; Grace Yao, PhD; and Wendy Lou
Kingston, New York; Hanover, New Hampshire; Boston, Massachusetts; New Haven, Connecticut

Background. Healthy people can have low levels of cobalamin (vitamin B_{12}) without symptoms or signs of cobalamin deficiency. Early detection of deficiency is imperative for treatment to be effective. Development of radioimmunoassay tests has greatly improved accurate determination of cobalamin (Cbl) levels. Nevertheless, results of studies of Cbl deficiency vary widely because of the variety of populations studied.
Methods. In a prospective study, we tested 100 consecutive, unselected geriatric outpatients in a primary care setting to determine the prevalence of cobalamin deficiency. All patients, 65 years of age or older, who visited the office of one of the authors during a period of 11 consecutive working days, had their serum Cbl level checked. If the level was 299 pg/mL or lower, serum intrinsic factor and parietal cell antibodies, serum gastrin, part 1 Schilling test, serum methylmalonic acid, and total homocysteine were done, when possible, for the diagnosis of type A gastritis and intracellular Cbl deficiency.
Results. Sixteen percent of geriatric outpatients had serum Cbl levels of 200 pg/mL or below, and 21% had levels between 201 and 299 pg/mL. Among the 16 patients with levels ≤200 pg/mL, 2 patients had macrocytic anemia, 3 patients had peripheral neuropathy, and 8 patients had type A gastritis. Among the 21 patients with levels of 201 to 299 pg/mL, 2 patients had peripheral neuropathy, 9 patients had type A gastritis, and none of the patients had macrocytic anemia. Among the patients whose methylmalonic acid and total homocysteine levels were determined, the results were high in 80% of those with Cbl levels ≤200 pg/mL and in 33% of those with levels from 201 to 299 pg/mL.
Conclusions. The prevalence of Cbl deficiency in geriatric outpatients was found to be higher than in any recent report. The lower limit of the normal range for Cbl level should be increased to 300 pg/mL.
Key words. Vitamin B_{12} deficiency; geriatrics; mass screening; prevalence studies.
J Fam Pract 1992; 35:524-528.

It is very important to diagnose cobalamin (Cbl) deficiency early because it is easily treatable.[1] A recent study[2] suggests that the window of opportunity for effective treatment of Cbl deficiency related to neuropsychiatric abnormalities may be as short as 1 year from the onset of symptoms. Neuropsychiatric abnormalities from Cbl deficiency are irreversible if treatment is started too late[3]; however, late treatment may prevent patients from getting worse.[3,4]

The determination of serum Cbl levels with the radioimmunoassay (RIA) technique has improved since 1978, when serum Cbl analogues were excluded.[5] The analogues gave erroneously high Cbl readings, thus causing false-negative results and missing approximately 20% of patients with confirmed Cbl deficiency.[6] The current RIA for determining Cbl is sensitive, relatively inexpensive, and widely available.[1]

It is well known, however, that healthy people can have low serum Cbl levels without symptoms or signs of Cbl deficiency. Conversely, patients with symptoms or signs of Cbl deficiency, who have responded to Cbl therapy, can have normal Cbl levels. Use of the serum Cbl assay for detection of Cbl deficiency is frequently insensitive even after the Cbl analogues are excluded.[6] The serum Cbl level varies according to serum Cbl–binding proteins and other factors.[1] The intracellular Cbl level controls Cbl-dependent metabolism. Serum methylmalonic acid and total homocysteine accumulate when intracellular Cbl deficiency is present. In the 1980s, Allen et al[6] found that the measurement of these serum metabolites was highly sensitive in the detection of intracellular Cbl deficiency.

Submitted, revised, August 24, 1992.

From the Department of Family Practice, New York Medical College, Kingston (Y.Y.), the Departments of Medicine and Family and Community Medicine, Dartmouth School of Medicine, Hanover, New Hampshire (L.Y., G.Y.), Department of Medicine, Boston University School of Medicine, Boston, Massachusetts (S.Y.), and Yale University School of Medicine, New Haven, Connecticut (W.L.). Requests for reprints should be addressed to Yulin Yao, MD, 1 Skytop Dr, Kingston, NY 12401.

ISSN 0094-3509

Table 1. Comparison of Studies* on Cobalamin Deficiency

Study	No. of Subjects	Subjects' Ages (y)	Definition of Cbl Deficiency	Reported Prevalence
Magnus et al, 1982[11]	217	>70	<133	16
Garry et al, 1984[12]	300	>60	<220	3
Barber et al, 1989[13]	100	>70	<183	23
Bunting et al, 1990[14]	250	>70	<200	2.4

**The patient populations varied between studies (nursing home, hospital) as did inclusion and exclusion criteria and level of cobalamin considered deficient. Cbl denotes cobalamin (vitamin B_{12}).*

In many patients, low serum Cbl levels are due to poor absorption of food or protein-bound Cbl. These patients have no difficulty absorbing crystalline Cbl. The results of Schilling tests are normal in these patients because the test uses crystalline Cbl. Carmel et al[7] found that 11 (58%) of 19 patients who had poor absorption of protein-bound Cbl had at least one of the following gastric dysfunctions: decreased gastric acid secretion (50%); elevated serum gastrin level (25%); and an abnormal pepsinogen ratio of 1:2 (40%), whereas in controls, 8 (31%) of 26 had gastric dysfunctions.

Antiparietal cell antibodies destroy the parietal cells and cause achlorhydria. In the absence of gastric acid, gastrin secretion is not inhibited and serum gastrin levels are elevated. Slingerland et al[8] reported that in a predominately male hospitalized population with an average age of 64 years, 7.7% had low levels of serum Cbl. Among them, 22% had elevated gastrin levels. Later, they also found that there is a low absorption of Cbl, either protein bound or unbound, in patients with low serum Cbl and high gastrin levels.[9]

In patients with pernicious anemia, approximately 90% have antibodies against parietal cells, 50% have antibodies against intrinsic factors, and 75% have elevated gastrin levels. These abnormalities, along with an abnormal Schilling test, have been referred to as type A (atrophic, fundal, or autoimmune) gastritis.[7–10]

The prevalence of Cbl deficiency in the elderly varies widely among previous published studies owing to the variable populations selected (Table 1).[11–14] Therefore, we studied consecutive geriatric outpatients to determine Cbl deficiency in a typical primary care setting.

Methods

The study took place in a private practice office of internal and geriatric medicine located in Ulster County (90 miles north of New York City, population 180,000), New York. During 11 consecutive working days between September 10, 1990, and September 24, 1990, there was a total of 100 patients 65 years of age or over (up to 93 years), who underwent serum Cbl testing. Fifty-nine women and 41 men constituted the subject population, with a mean age of 77 years. Included in this group were 97 white patients, 1 Japanese, 1 Hispanic, and 1 black patient. The majority of the patients were from the upper-middle socioeconomic class (income above the national average). All the patients who were studied presented because of acute or chronic diseases.

A history of paresthesia, the physical sign of vibration–joint position sensations, and the results of a Mini-mental State examination[15] were recorded in all patients. Peripheral neuropathy was defined as parasthesia with abnormal vibration and joint position sensations. Intracellular Cbl deficiency was confirmed in patients who had normal renal function, elevated serum methylmalonic acid, and/or total homocysteine.[1] Type A gastritis was diagnosed according to the following criteria: (1) no clinical evidence of gastric hyperacidity; (2) not taking H_2 blocker or omeprazole; (3) low Cbl levels coupled with increased antiparietal cell antibody titers, positive intrinsic factor antibody, elevated gastrin level, and/or abnormal results on the part 1 Schilling test.[7–10]

All laboratory work was performed by MetPath (Teterboro, NJ). The Cbl assay kits do not report serum Cbl levels below 100 pg/mL because of the insufficient sensitivity of the radioimmunoassay test below this level. Radioimmunoassay kits were obtained from Corning Diagnostics (Medfield, Mass). Serum methylmelonic acid and total homocysteine were done by the method of Allen and colleagues.[6,16]

Results

The average serum Cbl level of these patients was 419 pg/mL with a range of ≤100 pg/mL to 1479 pg/mL. There were 16 patients with serum Cbl levels at ≤200 pg/mL and 21 patients with Cbl levels between 201 and 299 pg/mL.

Results of the part 1 Schilling test and those for tests of methylmalonic acid and total homocysteine were not available for some patients because three patients died, three patients relocated, and one patient was given Cbl therapy before the study was completed. In addition, Medicare refused to pay for the tests of serum methylmalonic acid and total homocysteine for some patients, so we had to restrict these tests in many other patients. The Schilling test was found to be insensitive in patients whose serum Cbl levels were above 240 pg/mL; therefore, the test was not performed on the last seven patients with serum Cbl levels between 268 to 299 pg/mL. The data gathered here, however, are adequate to outline the causes of Cbl deficiency in most cases.

Table 2. Laboratory Findings and Clinical Diagnoses in Patient with Serum Cobalamin (Cbl) Levels Below 300 pg/mL.

Laboratory Test or Clinical Diagnosis	Indications of Cbl Deficiency	Frequency of Abnormal Results Found Among Patients* with Cobalamin Levels	
		≤200 pg/mL (n = 16)	201–299 pg/mL (n = 21)
Intrinsic factor antibodies	Positive	1/16	2/21
Parietal cell antibodies	>1:20	3/16	0/21
Fasting gastrin levels	>100 pg/mL	7/16	8/21
Part 1 Schilling test	<8% absorption	2/12	4/12
Type A gastritis	By criteria	8/16	9/21
Methylmalonic acid	>270 nmol/mL	4/5	3/9
Total homocysteine	>16 nmol/mL	3/5	1/9
Peripheral neuropathy	By criteria	3/16	2/21
Macrocytic anemia	MCV >100	2/16	0/21

**Average age of patients with cobalamin levels <200 pg/mL was 78 years and of patients with levels from 201 to 299 pg/mL was 76.5 years.*
Not all tests were performed on all patients; therefore, the denominators vary.
MCV denotes mean corpuscular volume.

Patients with low Cbl levels were more likely to have macrocytic anemia and peripheral neuropathy ($P < .01$), as shown in Table 2. This table also suggests that the prevalence of Cbl deficiency increases with age and that Cbl-deficient patients may live just as long as normal individuals, although the P values here were not significant. More studies are needed in this area. Patients with Cbl levels above 299 pg/mL were not tested for type A gastritis.

Among 16 patients with Cbl levels ≤200 pg/mL, 1 patient had Cbl-deficiency–related dementia, 1 had alcoholism-induced macrocytic anemia, 2 had Cbl-deficiency–induced macrocytic anemia, and 3 had peripheral neuropathy. Thirteen of the 16 patients were not anemic. Also among this group, 1 patient had positive intrinsic antibodies, 3 had elevated parietal cell antibody titers, 7 had high fasting gastrin levels, and 2 of the 12 patients tested had abnormal Schilling tests. Furthermore, of the 16 patients, 8 had type A gastritis, and 4 of the 5 patients tested had intracellular Cbl deficiency. In this group with Cbl levels ≤200 pg/mL, 1 patient had been given a Cbl injection before serum metabolites could be checked. Also, in 1 patient no clinical or laboratory abnormality for the diagnosis of type A gastritis, intracellular Cbl deficiency, or other known medical disease was found (Table 2).

In the group of 21 patients with Cbl levels from 201 to 299 pg/mL, 2 had peripheral neuropathy, 2 had positive intrinsic factor antibodies, and 8 had elevated fasting gastrin levels. Four of 12 patients tested had abnormal results on the Schilling test. Among these 4 patients, 2 had malabsorption. In this group of 21 patients, 9 had type A gastritis and 3 of the 9 patients tested had intracellular Cbl deficiency. In 8 of the 21 patients, no clinical or laboratory abnormality tested for in this study for the diagnosis of type A gastritis, intracellular Cbl deficiency, or other known medical disease was found. Furthermore, no one in this group had elevated parietal cell antibody titers or macrocytic anemia (Table 2).

Discussion

This prospective observational study demonstrates a high prevalence of Cbl deficiency among geriatric outpatients. Compatible results were found in a study by Barber et al[13] in 1989 in which 23% of a group of subjects over 70 years of age in rest homes and hospital geriatric wards had serum Cbl levels below 183 pg/mL.

Of the two patients with macrocytic anemia among those with Cbl levels ≤200 pg/mL, one had a Cbl level below 100 pg/mL and the other had a level of 130 pg/mL. Five patients with peripheral neuropathy had Cbl levels from below 100 to 258 pg/mL. These five patients and the rest of the 30 patients with Cbl levels below 300 pg/mL were not anemic with the exception of one patient with alcoholism.[7,8,17,18] Neuropsychiatric disorders due to Cbl deficiency occur commonly in the absence of macrocytic anemia.[7,17,18] A complete blood count is therefore an insensitive screening test for Cbl deficiency.

Bunting et al[14] found that 8 out of 250 patients over the age of 70 years admitted to a rehabilitation hospital had Cbl malabsorption. Among these 8 patients, 3 were positive for intrinsic factor antibody. Of those 3 patients, 1 had an abnormal serum Cbl level of 176 pg/mL and 2 had normal Cbl levels of 221 and 870 pg/mL. In our study, 1 patient in the group with Cbl levels of ≤200 pg/mL and 2 patients from the other group had positive intrinsic factor antibodies. Parietal cell antibody titers were elevated in 3 patients from the group with lower Cbl values. These incidences of intrinsic factor and pari-

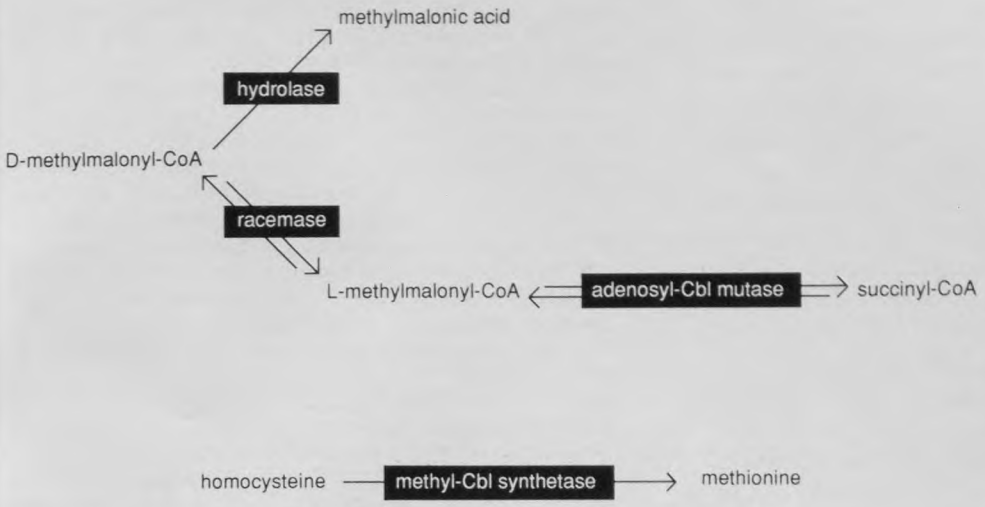

Figure 1. Adenosyl-Cbl mutase and methyl-Cbl synthetase are the two human Cbl-dependent enzymes.
Top: In Cbl deficiency, L-methylmalonyl-CoA accumulates and is converted back to D-methylmalonyl-CoA, which is hydrolyzed to methylmalonic acid.
Bottom: The other Cbl-dependent enzyme, methyl-Cbl-synthetase, normally converts homocysteine to methionine. In Cbl deficiency, this conversion is not possible. (Cbl denotes cobalamin.)

etal cell antibodies were much lower than textbooks describe because most incidences in textbooks are based on patients with pernicious anemia, whereas the great majority of our patients were not anemic.

Neither intrinsic factor nor parietal cell antibodies are particularly useful for establishing the diagnosis of Cbl deficiency because they do not indicate the status of intracellular Cbl metabolism. In addition, their sensitivities are very low. This is also true with part 1 of the Schilling test.[6,7]

Among 16 patients in the group with Cbl levels ≤200 pg/mL, 7 had elevated fasting gastrin levels and 8 could be classified with type A gastritis. Among 21 patients in the higher Cbl group, 8 had elevated fasting gastrin levels and 9 could be classified with type A gastritis.[7–10] The incidence of hypergastrinemia among our patients with low Cbl levels is higher than in both groups of patients reported by Carmel et al[7] and Slingerland et al.[8] The reasons for these differences could be because our patients were much older and the laboratory standards were different.

In the 1950s, Cox and White measured methylmalonic acid excretion in patients with Cbl deficiency.[19] In the 1980s, Allen and co-workers developed sensitive methods for serum methylmalonic acid and total homocysteine measurements.[6,16] Later, they suggested that 95% of Cbl-deficient patients had elevated serum methylmalonic acid and total homocysteine levels. The measurements of methylmalonic acid and total homocysteine are now recommended for the optimal diagnosis of Cbl deficiency.[1,20] Most patients with serum Cbl levels below 300 pg/mL do not show objective hematological or neuropsychiatric improvements with Cbl therapy if their serum methylmalonic acid and total homocysteine levels are normal.[16] The measurement of serum methylmalonic acid and total homocysteine are the most important recent developments for studying Cbl deficiency (Figure 1).

In our study, among the patients whose serum Cbl levels were below 200 pg/mL, 5 had serum methylmalonic acid and total homosycteine measurements, 4 had elevated methylmalonic acid levels, and 3 had elevated total homocysteine levels. Lindenbaum et al[16] reviewed the records of 419 Cbl-deficient patients and found that 12 (2.8%) of them had serum Cbl levels above 200 pg/mL, and their serum methylmalonic acid and total homocysteine levels were both elevated. In the group of patients with serum Cbl levels between 201 and 299 pg/mL, 9 patients had tests to determine methylmalonic acid and total homocysteine levels. Three of these patients had an elevated methylmalonic acid level and 1 had an elevated total homocysteine level.

Serum methylmalonic acid and total homocysteine measurements are not only more sensitive than Cbl measurement in the detection of early intracellular Cbl deficiency, but their measurements can also detect the adequacy of Cbl replacement and differentiate between megaloblastic anemias caused by Cbl deficiency and those caused by folate deficiency.[1,6,16,20]

Stabler et al[20] estimated that 5% to 10% of Cbl-deficient patients have serum Cbl levels between 200 and 300 pg/mL, and that 0.1% to 1% of Cbl-deficient patients have Cbl levels higher than 300 pg/mL. Lindenbaum et al[16] reported a group of 12 patients whose serum Cbl levels were between 215 and 475 pg/mL and who subsequently responded hematologically to Cbl therapy. Therefore, patients can have intracellular Cbl deficiency with normal serum Cbl levels. The reverse is also true: patients can have low serum Cbl levels without

intracellular Cbl deficiency. Serum Cbl levels are influenced greatly by binding proteins and by other factors.[1] Among clinically confirmed Cbl-deficient patients, approximately 50% had Cbl levels below 100 pg/mL, 40% between 100 and 200 pg/mL, 10% between 200 and 300 pg/mL, and 0.1% to 1% above 300 pg/mL.[1]

Among our patients who had abnormal methylmalonic acid and total homocysteine tests, the highest Cbl reading was 238 pg/mL. Many patients with higher Cbl levels, however, were not tested for these metabolites during our study. Among the patients who had type A gastritis, the highest Cbl level was 296 pg/mL.

Allen and colleagues[6,16,20] suggest that the appropriate lower limit of normal serum Cbl level is approximately 300 pg/mL. Our data strongly support this lower limit for normal in order to increase the sensitivity of Cbl screening.

We suggest that serum Cbl screening be done for every person aged 65 or older. If a level below 300 pg/mL is detected, serum levels of methylmalonic acid and total homocysteine should be checked, especially in those patients with unexplained hematological and neuropsychiatric disorders. If these metabolites are normal, annual follow-up is advisable. Further study and Cbl therapy is indicated if any of the results is abnormal. Methylmalonic acid and total homocysteine should also be checked in those patients who are clinically suggestive of Cbl deficiency even though their serum Cbl levels are above 300 pg/mL. Tests for both serum methylmalonic acid and total homocysteine are expensive ($273.90 from MetPath on Dec 1, 1991). However, the costs of late treatment of irreversible neuropsychiatric disorders from Cbl deficiency are vastly higher. Further studies are needed to determine whether serum Cbl screening should be started at a younger age.

Acknowledgment

We are indebted to John Lindenbaum, MD, for his many invaluable suggestions and to John Martine, Jayne Velie, and Jean Franke for their assistance.

References

1. Allen RH. Megaloblastic anemia. In Wyngaarden JB, Smith LH Jr, Bennett JC, eds. Cecil textbook of medicine. 19th ed. Philadelphia: WB Saunders, 1992:846–54.
2. Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. J Am Geriatr Soc 1992; 40:168–72.
3. Beck WS. Neuropsychiatric consequences of cobalamin deficiency. Adv Intern Med 1991; 36:33–56.
4. Hector M, Burton J. What are the psychiatric manifestations of vitamin B-12 deficiency? J Am Geriatr Soc 1988; 36:1105–12.
5. Kolhouse JF, Kondo H, Allen NC, Podell E, Allen RH. Cobalamin analogues are present in human plasma and can mask cobalamin deficiency because current radioisotope dilution assays are not specific for true cobalamin. N Engl J Med 1978; 299:785–92.
6. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Diagnosis of cobalamin deficiency. I: usefulness of serum methylmalonic acid and total homocysteine concentrations. Am J Hematol 1990; 34:90–8.
7. Carmel R, Sinow RM, Siegel ME, Samloff IM. Food cobalamin malabsorption occurs frequently in patients with unexplained low serum cobalamin levels. Arch Intern Med 1988; 148:1715–9.
8. Slingerland DW, Carlarelli JA, Burrows BA, Miller A. The utility of serum gastrin levels in assessing the significance of low serum B_{12} levels. Arch Intern Med 1984; 144:1167–8.
9. Miller A, Slingerland DW, Cardarelli JA, Burrows BA. Further studies on the use of serum gastrin levels in assessing the significance of low serum B_{12} levels. Am J Hematol 1989; 31:194–8.
10. Soll AH. Gastritis. In: Wyngaarden JB, Smith LH Jr, Bennett JC, eds. Cecil textbook of medicine. 19th ed. Philadelphia: WB Saunders, 1992; 648–52.
11. Magnus EM, Bache-Wiig JE, Aaderson TR, Melbostad E. Folate and vitamin B-12 (cobalamin) blood levels in elderly persons in geriatric homes. Scand J Haematol 1982; 28:360–6.
12. Garry PJ, Goodwin JS, Hunt WC. Folate and vitamin B_{12} status in a healthy elderly population. J Am Geriatr Soc 1984; 32:719–26.
13. Barber KE, Christie ML, Thula R, Cutfield RG. Vitamin B_{12} concentrations in the elderly: a regional study. N Z Med J 1989; 102:406–8.
14. Bunting RW, Bitzer AM, Kenney RM, Ellman L. Prevalence of intrinsic factor antibodies and vitamin B_{12} malabsorption in older patients admitted to a rehabilitation hospital. J Am Geriatr Soc 1990; 38:743–7.
15. Folstein MF, Folstein S, McHugh PR. Mini-mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–98.
16. Lindenbaum J, Savage DG, Stabler SP, Allen RH. Diagnosis of cobalamin deficiency II: relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. Am J Hematol 1990; 34:99–107.
17. Carmel R. Pernicious anemia, the expected findings of very low serum cobalamin levels, anemia, and macrocytosis are often lacking. Arch Intern Med 1988; 148:1712–4.
18. Lindenbaum J, Healton EB, Savage D, Brust JCM, Garrett TJ, Podell ER, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988; 318:1720–8.
19. Cox EV, White AM. Methylmalonic acid excretion: an index of vitamin B_{12} deficiency. Lancet 1962; 2:853–6.
20. Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. Blood 1990; 76:871–81.