Challenges in the Identification of Cobalamin-Deficiency Polyneuropathy

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Background: Diagnosing cobalamin (Cbl) deficiency as a cause of polyneuropathy (PN) is problematic, as the frequency of both disorders increases with age, and serum Cbl levels can be difficult to interpret.

Objectives: To identify unique clinical or laboratory features among PN patients with Cbl deficiency and to examine the role of testing of serum metabolite levels in the identification of Cbl deficiency.

Design: Cohort survey comparing patients with Cbl deficiency and cryptogenic PN identified during a 2-year period. Cobalamin deficiency was diagnosed using low serum Cbl levels or elevated serum metabolite levels.

Setting: Academic neuromuscular clinic.

Results: Of 324 PN patients, 27 were diagnosed as having Cbl deficiency. Twelve had Cbl levels within the normal range, but elevated serum metabolite levels. Compared with patients with cryptogenic sensory/sensorimotor PN, those with Cbl deficiency were more likely to have concomitant involvement of the upper and lower extremities and experience symptom onset in the hands and a sudden onset of symptoms ($P<.005$). These differences were seen regardless of whether Cbl deficiency was defined using low Cbl levels or elevated serum metabolite levels. Autoimmune pernicious anemia was identified in 6 (50%) of 12 Cbl-deficient patients with normal serum Cbl levels. The patients with PN and Cbl deficiency showed little objective improvement after parenteral replacement therapy; however, progression occurred less often in these patients compared with those with cryptogenic sensory/sensorimotor PN ($P = .02$).

Conclusions: This study highlights the challenges of proving that Cbl deficiency is the cause for PN and identifies clinical features that suggest Cbl-deficiency PN. Testing of serum metabolite levels may identify Cbl deficiency in some patients with normal serum Cbl levels.

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Although polyneuropathy (PN) is an established complication of deficiency of cobalamin (Cbl) (vitamin B$_{12}$), there are a number of uncertainties surrounding the PN of Cbl deficiency. For example, it is controversial whether PN can present in the absence of myelopathy. Also uncertain is the optimal laboratory approach to the diagnosis of Cbl deficiency.

Resolving these uncertainties is difficult for several reasons. Identifying Cbl deficiency in patients with PN (hereafter referred to as PN patients) does not necessarily prove that Cbl deficiency is the cause of the PN. Cobalamin deficiency and cryptogenic PN both occur with increased frequency in older individuals. In approximately 20% of patients presenting with sensory or sensorimotor PN, no cause can be identified, and these cases are referred to as cryptogenic sensory/sensorimotor PN (CSPN). If Cbl deficiency was simply coincidental in patients with CSPN (hereafter referred to as CSPN patients), the clinical and electrophysiologic features of the neuropathy should be the same as those observed in CSPN patients without Cbl deficiency. A finding of significant differences between PN patients with Cbl deficiency and CSPN patients suggests that Cbl deficiency was the cause of the neuropathy.

Some evidence suggests that commonly used assays of serum Cbl are not sufficiently sensitive to be the ideal method of diagnosing Cbl deficiency. Testing the levels of serum metabolites methylmalonic acid (MMA) and homocysteine (Hcy) may improve the identification of Cbl-deficient patients. Many advocate using elevated MMA and Hcy levels to diagnose Cbl deficiency,
even when serum Cbl levels are within normal limits.\textsuperscript{12,13}

These uncertainties pose problems for the clinician attempting to determine how aggressively to pursue the diagnosis and treatment of Cbl deficiency in patients presenting with what appears to be CSPN. The most definitive proof of Cbl-deficiency PN would come from a prospectively evaluated, objective improvement in response to Cbl replacement therapy. However, the literature provides conflicting information regarding how well Cbl-deficiency PN patients improve in response to replacement therapy.\textsuperscript{11,14}

In an attempt to address these questions, we investigated how often Cbl deficiency might be a cause of PN. We compared PN patients with definite or possible Cbl deficiency and CSPN patients with respect to clinical, laboratory, and electrophysiologic features. The yield of a serum Cbl assay was compared with that of tests of serum metabolite levels.

**METHODS**

We reviewed records from patients undergoing evaluation for sensory or sensorimotor PN during a 2-year period at a single university-based neuromuscular clinic (The University of Texas Southwestern Medical Center, Dallas). A patient was considered to have PN on the basis of clinical criteria previously devised for CSPN.\textsuperscript{9} Levels of serum Cbl and antimicrobial antibodies and erythrocyte sedimentation rate were measured, and complete blood cell count, chemistry profile, thyroid function tests, serum protein electrophoresis, immune-fixation electrophoresis, and serological testing for syphilis were performed for all PN patients. If the Cbl level was no greater than 300 pg/mL (221 pmol/L), serum MMA and Hcy levels were measured. If the MMA or Hcy level was elevated, serum was tested for anti-intrinsic factor and anti-parietal cell antibodies and gastrin levels. Pernicious anemia was diagnosed if anti-intrinsic factor antibodies were present or if anti-parietal cell antibodies were present with an elevated serum gastrin level.\textsuperscript{7} We measured MMA and Hcy levels in some cases in which the Cbl level was greater than 300 pg/mL if there were risk factors for malabsorption or clinical signs suggestive of Cbl deficiency (eg, brisk reflexes in the setting of PN).

Cobalamin deficiency was defined on the basis of specific constellations of laboratory abnormalities. If the serum Cbl level was less than 211 pg/mL (116 pmol/L) (the lower reference limit used by the laboratory processing the sample, hereafter referred to as normal), a diagnosis of Cbl deficiency was made only if MMA or Hcy levels were elevated. A patient with a serum Cbl level of 211 pg/mL or greater could be diagnosed as having Cbl deficiency under the following 2 conditions: (1) an elevated MMA level, or (2) an elevated Hcy level plus the presence of anti-intrinsic factor antibodies or the presence of anti-parietal cell antibodies plus an elevated serum gastrin level.\textsuperscript{7}

Among PN patients determined to have Cbl deficiency by these criteria, if no other cause of PN was identified, Cbl deficiency was considered to be the cause of the neuropathy. When Cbl deficiency was diagnosed, the patient was treated with intramuscular cyanocobalamin, 1000 µg/wk, for 4 weeks followed by 1000 µg each month thereafter.

We compared the PN patients with Cbl deficiency with CSPN patients.\textsuperscript{9} The CSPN patients used for comparison represented consecutive cases identified at the same neuromuscular center during the same 2-year period.

Portions of the neurological examination were quantified using an ordinal scoring system. Stretch reflexes were graded as follows: 3 indicated brisk; 2, normal; 1, decreased; and 0, absent. Light touch, pinprick, vibration, and joint position sensation were graded using a previously described scoring system.\textsuperscript{15} Using this system, the maximal possible total score is 28.

During the study period, 27 potential cases of Cbl-deficiency PN were identified from a total of 324 PN patients (8%; 95% confidence interval [CI], 5%-11%). Fifteen had low serum Cbl levels and normal serum metabolite levels. Twelve had normal serum Cbl levels and abnormal serum metabolite findings suggestive of Cbl deficiency. An alternate cause of PN was not detected in any of these patients. None of these cases had upper motor neuron findings such as extensor plantar responses, spasticity, clonus, or a sensory level. During the same period, 70 CSPN patients were identified (22%). The demographic and clinical features of the groups are summarized in Table 1. The CSPN patients had a longer duration of illness than the Cbl-deficiency PN patients. Cobalamin-deficiency PN patients were significantly less likely to have pain or lower limb weakness and more likely to have concomitant involvement of the upper and lower extremities. They were 22 times more likely to experience symptom onset in the hands or in the hands and feet simultaneously. A sudden onset of neuropathy symptoms occurred in 8 Cbl-deficiency PN patients and none of the CSPN patients (P < .001). There were no significant differences between the examination scores of the 2 groups. The incidence of brisk stretch reflexes was also not significantly different between groups. In the multivariate logistic regression model, 3 variables were significant. Pain and lower extremity weakness occurred less often in the Cbl-deficiency PN patients, whereas concomitant upper and lower extremity involvement occurred more often in Cbl-deficiency PN patients.

Laboratory test results are summarized in Table 2. Although Cbl-deficiency PN patients were significantly more likely to have erythrocytes with elevated mean corpuscular volumes, the incidence of anemia (decreased hematocrit level) did not differ. Folate levels and renal function were normal in all Cbl-deficient patients. Among the PN patients determined to have Cbl deficiency, the Cbl level was less than 300 pg/mL in all cases, except 3 patients in whom it was 328, 392, and 457 pg/mL (242, 289, and 337 pmol/L, respectively). Levels of MMA were elevated in all 3 of these cases, and Hcy levels were also elevated in 2.

There were no significant differences between Cbl-deficiency PN patients with low serum Cbl levels com-
pared with those with normal Cbl levels. A comparison of Cbl-deficiency PN patients with normal Cbl levels and CSPN patients yielded findings similar to those observed in the comparison of all Cbl-deficiency PN and CSPN patients, ie, the same clinical features were significantly different (Table 1). The laboratory features of Cbl-deficiency PN patients with low serum Cbl levels are compared with those with normal serum Cbl levels in Table 3. Levels of MMA were higher in patients with Cbl deficiency than in patients with CSPN. The mean duration of treatment was 11.5 months (range, 1-34 months). Five treated patients (24%) had gastrointestinal tract symptoms or disorders that might account for Cbl malabsorption. Of these, 2 were status post gastrectomy, 1 had symptoms of gastritis and chronic diarrhea, 1 had chronic pancreatitis, and 1 received long-term therapy with a histamine blocker. None of the Cbl-deficiency PN patients was a vegetarian. Of the 12 patients for whom no cause for Cbl deficiency was identified, all but 1 were older than 50 years (mean age, 68 years).

Eight Cbl-deficiency PN patients (30%) exhibited a sudden onset of their PN symptoms. Four of these had pernicious anemia. In 2 of the 8 patients, the onset of symptoms began after a surgical procedure for which general anesthesia and nitrous oxide were used. The NCS findings were abnormal in 70% of Cbl-deficiency PN patients. Compared with CSPN patients, Cbl-deficiency PN patients were more likely to have normal NCS findings. Overall, specific abnormal NCS findings were similar between the 2 groups. When abnormal NCS findings indicated axonal PN. No patient in either group had NCS findings that met criteria for demyelination. Electromyography was more likely to show evidence of denervation in CSPN patients, but this difference was not significant. The findings of quantitative sensory testing were abnormal in more than 80% of patients in both groups. The percentages of abnormal cold or vibration detection thresholds did not differ between groups. The findings of quantitative sensory testing were abnormal in the setting of normal NCS and electromyography findings in 1 patient from each group. The SEPs were normal in 6 of 12 patients. The abnormal findings in each of these cases indicated a lesion in the posterior columns of the spinal cord. Evoked potentials were not obtained for any of the CSPN patients.

Follow-up data were available for 21 Cbl-deficiency PN patients after treatment with parenteral cyanocobalamin. The mean duration of treatment was 11.5 months (range, 1-34 months). Five treated patients (24%) without pernicious anemia, 5 had gastrointestinal tract symptoms or disorders that might account for Cbl malabsorption. Of these, 2 were status post gastrectomy, 1 had symptoms of gastritis and chronic diarrhea, 1 had chronic pancreatitis, and 1 received long-term therapy with a histamine blocker. None of the Cbl-deficiency PN patients was a vegetarian. Of the 12 patients for whom no cause for Cbl deficiency was identified, all but 1 were older than 50 years (mean age, 68 years).

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reported improvement; in 2 of these it was considered marked. However, only 2 patients had objective findings of improvement on results of examination. There were no significant differences between the patients who improved vs those who did not with respect to the duration of symptoms or treatment. Thirty-eight CSPN patients were followed up for a mean duration of 8 months (range, 1-39 months). None of these showed objective improvement, and 12 (32%) manifested objective progression. There was a trend for less objective progression in the Cbl-deficiency PN patients (n=2 [10%]) compared with CSPN patients (32%; P=.057). In a multivariate model that adjusted for age and duration of symptoms, Cbl-deficiency PN patients (receiving cyanocobalamin replacement therapy) were less likely to manifest objective progression (P=.02).

Table 3. Comparison of Cbl-Deficiency PN Patients With Low vs Normal Serum Cbl Levels

<table>
<thead>
<tr>
<th>Low Serum Cbl Level (n = 15)</th>
<th>Reference Range Serum Cbl Level (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cbl, mean (range), pg/mL†</td>
<td>161.0 (30-210)</td>
<td>295.0 (232-457)</td>
</tr>
<tr>
<td>Serum MMA, mean (range), µmol/L‡</td>
<td>4.0 (0.13-51.0)</td>
<td>0.90 (0.29-3.8)</td>
</tr>
<tr>
<td>Serum Hcy, mean (range), µmol/L§</td>
<td>22.8 (11.0-40.0)</td>
<td>25.3 (16.0-40.0)</td>
</tr>
<tr>
<td>Abnormal MMA level, No. (%) of patients</td>
<td>12 (80)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Abnormal Hcy level, No. (%) of patients</td>
<td>12 (80)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Pernicious anemia, No. (%) of patients</td>
<td>4 (27)</td>
<td>6 (50)</td>
</tr>
</tbody>
</table>

Abbreviations: Cbl, cobalamin; Hcy, homocysteine; MMA, methylmalonic acid; PN, polyneuropathy.

SI conversion factors: To convert Cbl to picomoles per liter, multiply by 0.738; to convert Hcy to micromoles per liter, multiply by 7.397.

†Normal values are within the reference limits used by the laboratory processing the samples.
‡Normal value for MMA level, <0.4 µmol/L.
§Normal value for Hcy level, <15 µmol/L.

Table 3 compares Cbl-deficiency PN patients with low vs normal serum Cbl levels. The table shows that patients with low serum Cbl levels had significantly lower levels of serum Cbl compared to those with normal Cbl levels.

**Comment**

Diagnosing Cbl deficiency as a cause of PN can be challenging. The presence of Cbl deficiency does not prove this to be the cause of the PN. We identified Cbl deficiency in 8% (95% CI, 5%-11%) of all patients referred to us with PN. Our findings are not strikingly different compared with 2 smaller series examining the etiology of PN. Cbl deficiency ranged from 2% to 6% (95% CI, 0%-10%), but neither series used serum metabolic testing.

One factor suggestive of Cbl deficiency being the cause of neuropathy in our patients is the distinct clinical differences between PN patients with Cbl deficiency and CSPN patients. Approximately one third of the Cbl-deficiency PN patients had a sudden onset of symptoms. This was not observed in any of the CSPN patients. Acute onset of neurological manifestations has been described in Cbl-deficient patients. This has been in the context of exposure to nitrous oxide (which is routinely administered with inhalational general anesthesia). For 2 of our patients with a sudden onset of symptoms, antecedent exposure to nitrous oxide (via general anesthesia) appears to be the cause. No clear precipitant was identified for the other 6 patients. The course, clinical features, and electrodiagnostic features of these cases did not suggest Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy.

Despite a shorter duration of symptoms, PN patients with Cbl deficiency were almost 2 times more likely than CSPN patients to have concurrent involvement of upper and lower extremities. Furthermore, symptoms began in the hands or in the hands and feet simultaneously in 6 of PN patients with Cbl deficiency (22%). Only 1 CSPN patient had concomitant involvement of hands and feet. Onset of sensory symptoms in the hands is often regarded as a manifestation of Cbl deficiency, and isolated hand findings may represent myelopathy. The non-length-dependent pattern observed in Cbl-deficiency PN patients may be due to spinal cord involvement, although no patient had physical examination findings indicative of myelopathy. Many of our Cbl-deficiency PN patients had SEPs indicating spinal cord lesions, but the significance of this finding is limited because SEPs were not obtained in the CSPN patients.

The PN patients with Cbl deficiency differed significantly from CSPN patients with respect to other clinical features (lower incidence of pain and lower extremity weakness), although none of these is distinct enough to impute Cbl deficiency in a patient presenting with PN. Despite no difference in sensory examination or stretch reflex findings, PN patients with Cbl deficiency had normal NCS findings significantly more often than did CSPN patients. When abnormal, NCS findings were similar between the 2 groups and showed an axonal neuropathy. The findings of quantitative sensory testing also did not distinguish between Cbl-deficiency PN and CSPN patients. Erythrocyte mean corpuscular volume was abnormally elevated in 12% of Cbl-deficiency patients (P=.008). A low incidence of hematologic abnormalities among Cbl-deficient PN patients presenting with neurologic manifestations has previously been noted. The patients we describe as having Cbl deficiency PN may have both PN and myelopathy or myelopathy alone (especially in the case of patients with normal NCS findings). On the basis of routine clinical evaluation, however, these patients appear to have only PN. Identification of myelopathy through diagnostic testing also has limitations. For these reasons, we have used the term Cbl-deficiency PN for this group.

The absence of vibration or proprioceptive sensory deficits in 5 (19%) of our patients diagnosed with Cbl-deficiency PN implies that concomitant myelopathy is not present in all cases. This contradicts standard teaching, which has suggested that deficits in large-fiber sensory function are present in patients with neurologic...
complications of Cbl deficiency. A problem is that most early studies, for the purpose of diagnostic certainty, tended to include mainly patients manifesting the features of subacute combined systems disease. Indeed, 1 study of the effect of liver extract treatment specifically excluded individuals with features of only PN.21

Some of the patients with normal serum Cbl levels may have been diagnosed as having Cbl deficiency as a false-positive finding, especially those with higher serum Cbl levels. Inclusion of patients with false-positive findings would dilute differences between true Cbl-deficient patients and those with CSPN. Removing those patients with serum Cbl levels of greater than 300 pg/mL did not change any of the results. In addition, patients with or without pernicious anemia did not differ from one another, and each of these groups showed the same significant differences compared with CSPN patients.

Concern about relying on MMA and Hcy levels to diagnosis Cbl deficiency is warranted because elevated levels of these metabolites can result from a number of causes. An elevated serum MMA level is rather specific for Cbl deficiency, but hypovolemia and renal insufficiency can produce abnormalities.22 Genetic disorders can also produce elevated MMA levels, but these are quite rare.22 Elevated serum Hcy levels are less specific for Cbl deficiency; hypovolemia, renal insufficiency, hypothyroidism, increased age, genetic factors, and deficiency of folic acid or vitamin B6 are common causes of elevated serum Hcy levels.22 For this reason, we only considered a patient with an elevated serum Hcy level to have Cbl deficiency if pernicious anemia could be diagnosed. Folate levels, thyroid function test results, volume status, and renal function test results were normal in all of our patients labeled as Cbl deficient. We did not repeat serum metabolite level measurements after initiating Cbl replacement therapy, but observing a decrease in MMA and Hcy levels after initiation of treatment could confirm that metabolite level elevations were truly secondary to Cbl deficiency.

The same significant differences between patients with Cbl-deficiency PN and CSPN were seen, regardless of whether Cbl deficiency was diagnosed on the basis of low serum Cbl or elevated serum metabolite levels. This provides support that patients with abnormal MMA or Hcy levels, but normal serum levels of Cbl, actually have Cbl deficiency. Six (50%) of 12 patients with normal Cbl levels but abnormal serum metabolite levels had pernicious anemia. Pernicious anemia was diagnosed in each of these patients on the basis of intrinsic factor antibodies, which are extremely specific.23 Finding this high incidence of pernicious anemia in patients with normal serum Cbl levels is unlikely to be a coincidence and strongly suggests that those patients truly had Cbl deficiency. In several series of healthy adults older than 60 years with serum Cbl levels of less than 300 pg/mL, the prevalence of anti–intrinsic factor antibodies did not exceed 2%.39,24

Improvement occurred in almost a quarter of Cbl-deficiency PN patients who received parenteral cyanocobalamin replacement therapy, although this improvement was largely subjective. Objective improvement was documented in 10% of these patients, but in none of the CSPN patients (P=.053). Cobalamin-deficiency PN patients receiving replacement therapy were 3 times less likely to show objective progression than CSPN patients. Our study design does not allow us to conclude that cyanocobalamin replacement therapy was responsible for the more favorable course of these patients compared with the CSPN group. A high frequency of improvement of neurological symptoms after cyanocobalamin replacement therapy has been described,1,21 but this finding is based on studies that assess all neurological complications of Cbl deficiency (central and peripheral nervous system). Among Cbl-deficiency PN patients, improvement, especially objective, occurs much less often.1 Some authors10 have noted a poor response of chronic Cbl-deficiency PN to replacement therapy.

The lack of a clear response of the Cbl-deficient PN patients to replacement therapy could be explained by a number of factors. This retrospective study was not designed to sufficiently assess treatment response. Inconsistent follow-up and small patient numbers could have caused a potential treatment response to be missed. The observed poor treatment response may have occurred because of the long duration of neuropathy symptoms experienced by our patients (mean, 3.6 years) before cyanocobalamin replacement therapy was initiated. Symptom duration appears to be a major determinant for the extent of neurological improvement after treatment.1,22 It is possible that cyanocobalamin replacement therapy needs to be started early for significant improvement in PN symptoms and findings to occur. It is plausible to speculate that cyanocobalamin replacement therapy might prevent neuropathy progression, even if it produced no obvious improvement. Confirming this hypothesis would require a prospective trial.

It has been suggested that, among individuals with serum Cbl levels within the normal range, testing of serum metabolite levels will reveal Cbl deficiency in 5% to 10% of those with a serum Cbl level of less than 300 pg/mL, and in 0.1% to 1% of those with a serum Cbl level of 300 pg/mL or greater.10 On this basis, some authors have recommended measuring MMA and Hcy levels in all PN patients with serum Cbl levels of less than 300 pg/mL.12 This proposal may be premature, but the findings of the present study suggest that a distinct entity of Cbl-deficiency PN exists and an appreciable proportion of these patients might require testing of serum metabolite levels for diagnosis.

A larger prospective study with more structured and prolonged monitoring of treatment response and more use of evoked potentials and spinal imaging is needed to definitively address many of these uncertainties. Nevertheless, if a patient presenting with clinical features suggestive of PN has a normal serum Cbl level that is less than 300 pg/mL, measurement of MMA and Hcy levels should be considered if the patient experienced the sudden onset of symptoms or has symptoms beginning in the hands, macrocytic red blood cells, features suggestive of myelopathy, or risk factors for Cbl malabsorption. If either serum metabolite level is elevated, a trial of parenteral cyanocobalamin replacement therapy might
be reasonable, especially if pernicious anemia is identified. A decrease in serum metabolite levels in response to cyanocobalamin replacement therapy would suggest true Cbl deficiency and justify sustained treatment.

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