

The Role of Vitamin B₁₂ in the Management and Optimization of Treatment in Patients With Degenerative Cervical Myelopathy

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Abstract

Study Design: Narrative review.

Objectives: To discuss the relationship between degenerative cervical myelopathy (DCM) and vitamin B₁₂ deficiency. Specifically, it is the aim to outline the rationale for future research into assessment and therapeutic optimization of vitamin B₁₂ in the treatment of DCM.

Methods: Literature review.

Results: DCM is the commonest cause of spinal cord impairment, with an average age of presentation in the sixth decade. Patients at this age have also been reported to have a high prevalence of vitamin B₁₂ deficiency, with estimates of up to 20% in the elderly. Vitamin B₁₂ deficiency can result in subacute combined degeneration of the spinal cord (SACD), and several case reports have pointed to patients with both DCM and SACD. Both SACD and reversible compressive injury due to DCM necessitate remyelination in the spinal cord, a process that requires adequate vitamin B₁₂ levels. Basic science research on nerve crush injuries have shown that vitamin B₁₂ levels are altered after nerve injury and that vitamin B₁₂ along with dexamethasone or nonsteroidal anti-inflammatory drugs can reduce Wallerian degeneration. Furthermore, it has been suggested that a combination of B-vitamins can reduce glutamate-induced neurotoxicity.

Conclusions: Given the high prevalence of clinical and subclinical vitamin B₁₂ deficiency in the elderly, the role of vitamin B₁₂ in myelination, and vitamin B₁₂ deficiency as a differential diagnosis of DCM, it is important to investigate what role vitamin B₁₂ levels play in patients with DCM in terms of baseline neurological function and whether optimization of vitamin B₁₂ levels can improve surgical outcome. Furthermore, the routine assessment of vitamin B₁₂ levels in patients considered for DCM surgery should be considered.

Keywords

nutrition, anemia, subacute combined degeneration, spinal cord, nitrous oxide, cobalamin

Introduction

Degenerative cervical myelopathy (DCM) encompasses a set of age-related changes of the cervical spine that result in spinal cord impairment through static and dynamic injury mechanisms.¹ Patients with DCM typically present with variable degrees of upper and lower limb neurological deficits, including numbness, clumsiness, gait impairment, and motor weakness. Additionally, objective myelopathic signs such as Hoffmann's sign, Babinski's reflex, and ankle clonus may be

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observed.^{2,3} One of the potential differential diagnoses to consider in these patients is cobalamin or vitamin B₁₂ (B₁₂) deficiency. Neurological deficits encountered with B₁₂ deficiency include peripheral neuropathy, myelopathy, mental status changes, optic neuropathy, or a combination of these.^{4,5} Patients with both DCM and B₁₂ deficiency are most frequently diagnosed above the age of 50 years, and it has been estimated that the prevalence of B₁₂ deficiency is about 20% in industrialized countries.⁴ Furthermore, many more patients may have subclinical B₁₂ deficiency.⁶ Given this high prevalence of B₁₂ deficiency in elderly population, it would seem intuitive that many patients with DCM are also affected. Indeed, there have been some case reports describing patients with DCM and superimposed B₁₂ deficiency.⁷⁻⁹ Investigation of this relationship is important since deficiency of B₁₂ may not only exacerbate myelopathic symptoms in DCM but may also hinder neurological recovery, since B₁₂ is essential for myelination.¹⁰ In this review, the mechanism of action, causes of deficiency, and presentation of B₁₂ deficiency will be briefly described and will be followed by the role of routine B₁₂ assessment and its potential role in optimizing surgical outcome in patients with DCM.

Vitamin B₁₂: Mechanism of Action

Vitamin B₁₂ is synthesized exclusively by anaerobic bacteria, and it is obtained in foods of animal origin. Uptake of B₁₂ in the gastrointestinal system requires binding of a glycoprotein called intrinsic factor, which is secreted by gastric parietal cells. The B₁₂-intrinsic factor complex binds to “cubam” receptors expressed on enterocytes in the distal ileum and is absorbed via receptor-mediated endocytosis. Given the critical role of intrinsic factor in B₁₂ uptake, deficiencies in the glycoprotein due to an autoimmune gastritis known as “pernicious anemia” leads to a severe B₁₂ deficiency, with hematological and neurological manifestations.¹¹

Intracellular B₁₂ is stored as 2 active coenzymes: methylcobalamin and deoxyadenosylcobalamin. Methylcobalamin acts as a coenzyme for cytoplasmic methionine synthase, which catalyzes the methylation of homocysteine to methionine. This transmethylation reaction also involves folate (vitamin B₉) and is therefore critical for nucleic acid synthesis. Deoxyadenosylcobalamin is a cofactor for methylmalonyl-CoA mutase, which catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA in the mitochondria. Succinyl-CoA subsequently enter the Krebs cycle and is important for the synthesis of lipids and carbohydrates¹² (Figure 1).

Methylcobalamin is also important for the synthesis and maintenance of the myelin sheath. A number of studies report the development of white-matter lesions or retarded myelination in patients with B₁₂ deficiency.¹³⁻¹⁵ Although the precise molecular mechanisms underlying methylcobalamin-mediated myelination are unknown, a number of models have been suggested, including increased synthesis of lecithin (the primary component of myelin sheath lipids)^{16,17}; downregulation of Erk1/2 and upregulation of myelin basic protein¹⁸; increased

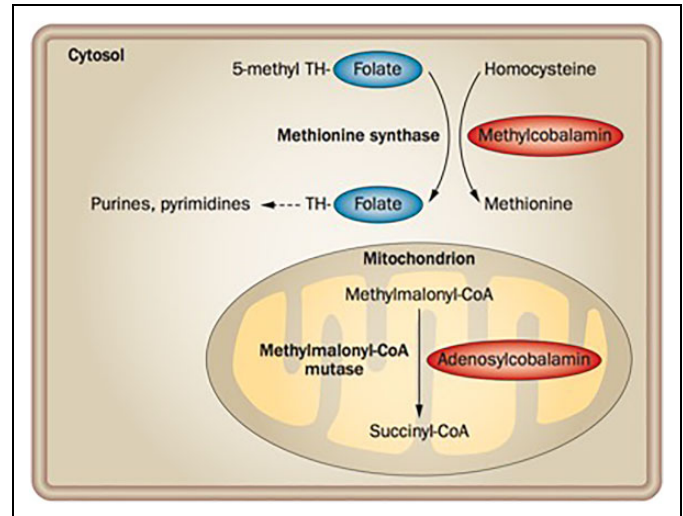


Figure 1. Vitamin B₁₂ coenzyme function. B₁₂ acts as a coenzyme in the conversion of homocysteine to methionine in the cytosol, and the conversion of methylmalonyl-CoA to succinyl-CoA in the mitochondrion. The cytoplasmic reaction requires folate, as the methyl group that is added to homocysteine is removed from 5-methyl tetrahydrofolate. Tetrahydrofolate is a precursor in the synthetic pathway for purines and pyrimidines, while succinyl-CoA enters the Krebs cycle and is important for lipid and carbohydrate synthesis. Reprinted with permission from Springer: *Nature Reviews Gastroenterology and Hepatology* (Nielsen et al¹¹).

synthesis of myelinotrophic cytokines and growth factors, such as IL-6 and EGF¹⁹; upregulation of neurotrophic gene factors²⁰; and regulation of normal prion protein concentration in the central nervous system.²¹

Vitamin B₁₂ Deficiency: Anemia, Neuropathy, and Myelopathy

Vitamin B₁₂ deficiency is a significant health concern in the United States; it is estimated that 5% to 40% of the elderly population have low serum B₁₂ levels.^{4,22-24} Due to enterohepatic circulation and kidney reabsorption, humans have extensive stores of B₁₂ and require several years of inadequate intake to present with a clinical deficiency. As a result, with the exception of unsupplemented populations of vegans, B₁₂ deficiency occurs primarily through gastrointestinal malabsorption.^{11,25} The most direct measurement of B₁₂ status is the measurement of total serum B₁₂. Laboratory ranges for normal (>221 pmol/L), low (148-221 pmol/L), and acute deficiency (<148 pmol/L) have been established and are used in most clinical settings.²² However, a major limitation of this assay is that it assesses total circulating B₁₂, about 80% of which is bound to haptocorrin, a transcobalamin protein, and not bioavailable.²⁵ Furthermore, a number of studies have shown that serum B₁₂ does not reliably represent levels of cellular B₁₂. As a result, assessing serum B₁₂ alone does not allow for an accurate diagnosis of deficiency.²⁵ A more effective method of diagnosis is to use serum B₁₂ measurements in conjunction with other biomarkers, namely, homocysteine (Hcy), methylmalonic acid

Table 1. Diagnostic Parameters, Reference Ranges, and Potential Confounding Factors for Assessment of Vitamin B₁₂ Deficiency^a.

Parameter	Reference Range	Confounding Factors
B ₁₂	>148 pmol/L	Renal insufficiency (↑)
Hcy	<15 μmol/L	Renal insufficiency (↑) Folate deficiency (↑) Vitamin B ₆ deficiency (↑)
MMA	<260 nmol/L	Renal insufficiency (↑) Age (↑) Intestinal bacterial overgrowth (↑)

Abbreviations: B₁₂, vitamin B₁₂; Hcy, homocysteine; MMA, methylmalonic acid.
^aAdapted from Hermann W, Obeid R. Cobalamin deficiency. In: Stranger O, ed. *Water Soluble Vitamins: Clinical Research and Future Application*. Berlin, Germany: Springer; 2012:301-322.

(MMA), and holo-transcobalamin (holo-TC). Hcy and MMA accumulation occurs as a result of inactivation of the 2 B₁₂-dependent enzymes, methionine synthase and methylmalonyl-CoA mutase, respectively. Most studies set the upper limit of normal plasma Hcy to 15 μmol/L; higher levels are indicative of a nutritional deficiency.²⁶ However, since the conversion of Hcy to methionine via methionine synthase also depends on the availability of folate, nutritional deficiencies in *either* folate or B₁₂ could result in increased levels of Hcy. MMA, on the other hand, is not affected by other vitamins and is therefore considered a more specific biomarker of B₁₂ deficiency. Serum levels of MMA that are greater than 260 nmol/L indicate an elevated reading²⁶ (Table 1). Notably, certain pathologies such as renal dysfunction may also present with increased levels of MMA; as a result, the use of this marker in elderly patients with renal disease should be done cautiously.²⁷ Last, Holo-TC, in contrast to haptocorrin, is the readily bioavailable form of B₁₂ transport, and is therefore a more accurate biomarker of B₁₂ status. The normal range of holo-TC is 20 to 125 pmol/L.²⁸ An algorithm for the diagnosis of B₁₂ deficiency using these 3 biomarkers in addition to serum B₁₂ was presented by Hannibal et al.²⁵

The Schilling test, an assay for pernicious anemia in which radiolabeled vitamin B₁₂ is ingested and its excretion measured in urine, is now rarely used in the United States. Two studies have shown that elevated levels of Hcy and MMA were detectable in 15% to 33% of patients with normal Schilling tests, indicating the increased specificity of laboratory measurements in diagnosing B₁₂ deficiency.^{29,30} Magnetic resonance imaging (MRI) is not normally indicated for patients with B₁₂ deficiency, but some reports have noted characteristic V-shaped hyperintensity on T2-imaging when present in the cervical cord and “bumbell” or bilateral nodular shape when present in the thoracic cord in patients with severe myelopathy^{31,32} (Figure 2).

The clinical presentations of B₁₂ deficiency include megaloblastic anemia and neurological deficits. Megaloblastic anemia is characterized by enlarged red blood cell precursors with asynchronous maturation of the nucleus and cytoplasm. The clinical picture of megaloblastic anemia develops slowly, and symptoms include weakness, palpitations, dyspnea on exertion, fatigue,

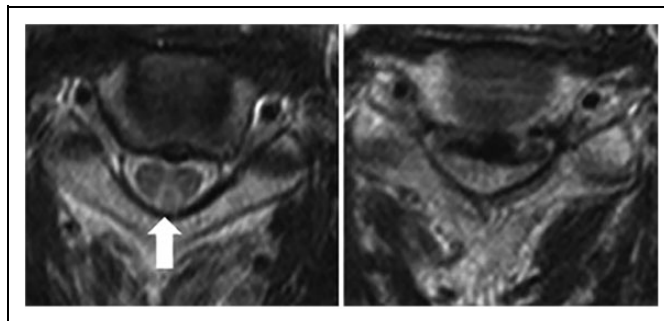


Figure 2. Axial T2-weighted MRI of a patient with degenerative cervical myelopathy and concomitant B₁₂ deficiency. On the left, a characteristic reverse V-shaped hyperintensity is visible in the posterior column (arrow). On the right significant spinal cord compression is demonstrated. Reprinted with permission from Elsevier: *The Spine Journal* (Miyazaki et al⁸).

light-headedness, jaundice, and shortness of breath. These symptoms typically do not arise until the anemia is quite severe, as cardiopulmonary adaptations can alleviate hypoxia.³³

Common neurological symptoms include myelopathy, neuropathy, and, less frequently, optic nerve atrophy.¹² The best characterized form of myelopathy is known as subacute combined degeneration (SACD). SACD is caused by damage to dorsal and lateral columns and is characterized by symmetric dysesthesia, abnormal proprioception, loss of vibratory sensation, positive Romberg sign, and spastic paraparesis or tetraparesis. Oftentimes, patients initially report sensory loss, presenting as lower limb paresthesia associated with ataxia. In late-stage disease, lateral corticospinal tracts can be involved, leading to impairment of fine motor function and abnormal reflexes.³⁴ Furthermore, a minority of patients present with autonomic disturbances, including bladder and erectile dysfunction.³⁵

Peripheral neuropathy is seen in approximately 25% of patients with B₁₂ deficiency.⁵ Symptoms include paresthesias, impaired sensation in a “glove and stocking” distribution, painful burning sensations, and muscle wasting.^{36,37} Occasionally, adult patients with B₁₂ deficiency will present with optic neuropathy, characterized by symmetric, painless, and progressive visual loss. Ophthalmologic findings include central and centrocecal scotomas.³⁵

Although hematologic signs often precede neurological symptoms, neurological symptoms may be the primary manifestation of B₁₂ deficiency in some patients. For example, studies by Lindenbaum et al³⁸ and Heaton et al⁵ showed that up to 28% of patients with neuropsychiatric symptoms of B₁₂ deficiency can present with normal mean corpuscular volume (MCV), hematocrit (HCT), or both. However, although HCT and MCV were normal in these reports, other hematological signs such as neutrophil hypersegmentation were found to be abnormal on inspection of peripheral blood smear.^{5,38,39} There have been reports of B₁₂-deficient patients with neurological symptoms *and* normal MCV, HCT, peripheral blood smear, and Hcy levels, although this is quite rare.⁴⁰

Table 2. Clinical Findings That May Appear on Examination in Patients With DCM.

Clinical Symptoms	Clinical Signs	MRI Findings
<ul style="list-style-type: none"> • Corticospinal motor deficits • Numbness of hands • Atrophy of hand muscles • Hyperreflexia and spasticity • Gait disturbances (broad based) • Clumsy hands • Weakness • Paraesthesia • Urinary incontinence (in severe cases) 	<ul style="list-style-type: none"> • Hoffmann sign • L'Hermitte's phenomenon • Ankle clonus • Babinski sign • Romberg sign 	<ul style="list-style-type: none"> • Cord compression • Cord flattening • Cord torsion • T2WI Cord hyperintensity • T1WI cord hypointensity

Pathophysiology of DCM

There are a number of pathophysiological factors that result in DCM: (1) static compression of the spinal cord, (2) dynamic injury resulting from mobile degenerative cervical spine elements compressing the cord, and (3) tethering of the cord or altered cord tension due to changes in the cervical spine alignment or cord compression.^{1,41} These various mechanisms contribute to spinal cord dysfunction by causing reversible and irreversible injury to neuronal tissue. Reversible tissue injury includes demyelination, Wallerian degeneration, edema, and inflammatory changes. Whereas irreversible injury manifests after frank loss of neuronal tissue has occurred.⁴² The underlying pathobiological mechanisms causing neuronal death are multifold. Mechanical compression initiates an inflammatory process that can be further exacerbated by disruption of blood flow and the blood-spinal cord barrier. Disruption of blood supply may result in variable degrees of cellular injury. This may be caused by direct blood vessel compression, as well as increased spinal cord tension, which may not only cause stretching of nerve fibers but also flattening of blood vessels.^{1,41,43} The degree of injury is highly variable and is affected by the degree of cord compression, the number of levels involved, and whether the compression is static or dynamic. Consequently, the natural history and clinical manifestations of DCM are highly variable. Clinically, patients typically present with problems using items with their hands and/or problems with their gait.³ In more severe cases, urine incontinence may also manifest. While diagnosis of DCM is based on clinical examination, imaging evidence of spinal cord compression or cord tethering on MRI is required to confirm the diagnosis (Table 2).

On MRI, patients typically present with one or more levels of cord compression. The direction of the compressive force typically originates from the anterior or anterior and posterior (pincer effect). In most, but not all patients, T2-weighted hyperintensity will approximate the site of cord compression, representing nonspecific inflammatory changes ranging from

edema to cavitation depending on the signal intensity and appearance.⁴² T1-weighted hypointensity changes can occur in approximately one fifth of DCM patients at the site of T2-weighted hyperintensity, indicating cavitation and that frank neuronal tissue loss has occurred.⁴²

Rationale for Investigating B₁₂ Deficiency in DCM

On the Basis of Epidemiology

Both B₁₂ deficiency and DCM are most prevalent in the elderly, and with estimates of 20% of B₁₂ deficiency, even a proportional prevalence among DCM patients would indicate a high rate of potential deficiency among the DCM population. Clinically, reports of patients with known B₁₂ deficiency and superimposed DCM have shown that patients appear with a degree of neurological impairment out of proportion of what would be expected based on imaging, and that treatment with B₁₂ can optimize neurological recovery.⁷⁻⁹ In other case reports, patients with suspected diagnosis of DCM, but underlying SACD, experienced a resolution of symptoms after B₁₂ administration.⁴⁴⁻⁴⁶ These findings have the following implications: patients with definitive DCM and concomitant B₁₂ deficiency require treatment for both conditions to optimize neurological recovery, but care should be taken for patients with mild cord compression and possible B₁₂ deficiency prior to surgical treatment, as cord compression may be a false positive finding and treatment with B₁₂ may resolve symptoms.

A high index of suspicion for B₁₂ deficiency among DCM patients should be placed among patient with history of gastrointestinal resection or comorbidities, such as atrophic gastritis and irritable bowel disease, which may be an underlying cause for unrecognized B₁₂ deficiency.⁴⁷ When suspected, laboratory findings of megaloblastic anemia, low B₁₂ levels, and high levels of homocysteine may be helpful.

On the Basis of Pathophysiology

The average patient receiving surgical treatment for DCM has moderate to severe neurological impairment at presentation,⁴⁸ and nonoperative management has been shown to result in neurological deterioration in 20% to 62% of patients at 3 to 6 years of follow-up.⁴⁹ When surgical treatment is undertaken, the average patient experiences meaningful neurological recovery.⁴⁸ However, not all patients experience significant improvement, others maintain their preoperative levels of function, and less commonly, patients experience neurological deterioration. The occurrence of suboptimal recovery can be expected since it is known that DCM can have elements of reversible and irreversible neuroanatomic changes—the balance of which influences the degree of functional recovery.⁵⁰ Approximately 80% of patients with DCM present with either no significant changes or only T2-weighted hyperintensity signal on conventional MRI,⁵⁰ and these MRI findings suggest that most patients have a large component of nonspecific

inflammatory changes, including Wallerian degeneration, that are potentially reversible. Reversible neurological function, however, is partly attributable to remyelination, which requires B₁₂.¹⁰ While there have been no direct clinical studies looking at B₁₂ and DCM, basic science research has shown that peripheral nerve crush injury alter the levels of B₁₂ at the nerve,⁵¹ and it has been suggested that B₁₂ with dexamethasone or nonsteroidal anti-inflammatory drugs can be used to treat peripheral nerve crush injury and reduce Wallerian degeneration.^{52,53} Sun et al⁵² suggested that upregulation of brain-derived neurotrophic factor (BDNF) may be a mechanism of action for this improvement.

Vitamin B₁₂ may also have a role in attenuating neurological deterioration after surgery for DCM. While the occurrence of deterioration is infrequent, not clearly understood, and difficult to anticipate, it has been suggested that reperfusion injury and subsequent glutamate excitotoxicity after cord decompression may be responsible for this phenomenon.^{54,55} It has been shown that treatment with a combination of B-vitamins (including B₁, B₆, B₁₂) can reduce neuronal injury,⁵⁶ and it has been suggested that B₁₂ potentially depresses glutamate-induced neurotoxicity.⁵⁷ These studies suggest that in addition to raising B₁₂ levels in those with suboptimal levels, higher levels may also provide a therapeutic benefit to patients receiving surgery for DCM. This however remains speculative.

On the Basis of Preoperative Planning

An intriguing and clinical relationship between B₁₂ and myelopathy that may be highly relevant for patients with DCM is also interaction of nitrous oxide (N₂O) during anesthesia with perioperative myelopathy development.⁴⁷ N₂O irreversibly oxidizes the cobalt ion at the center of B₁₂, and impedes its crucial cofactor function for methionine synthetase. This enzyme is required for the formation of tetrahydrofolate (THF) and methionine. THF is involved in thymidine synthesis and DNA production, while methionine is required for the methylation of myelin sheath phospholipids.⁵⁸ Consequently, patients with already low levels of B₁₂ or methylene-tetrahydrofolate-reductase deficiency are particularly at risk for perioperative myelopathy due to N₂O administration.⁵⁸ Although rare and an underrecognized phenomenon, there have been numerous case reports describing the development of SACD after anesthesia with N₂O administration.^{47,59-62} Given that N₂O can be used during spine surgery, this points to the necessity of routinely monitoring B₁₂ levels in patients with DCM to optimize surgical outcomes and prevent perioperative or postoperative neurological deficit development. Recognition of this phenomenon is important, as intramuscular injection of B₁₂ has been shown to rapidly reverse SACD symptoms.⁴⁷

Conclusion

It is clear that B₁₂ is necessary for maintaining spinal cord function, and deficiency can result in SACD. Given the high prevalence of clinical and subclinical B₁₂ deficiency in the

elderly, the role of B₁₂ in myelination, and B₁₂ deficiency as a differential diagnosis of DCM, there is considerable rationale to conduct routine assessment of B₁₂ levels in patients with DCM. Going forward, it will be necessary to assess additional aspects of this relationship, including (1) whether DCM patients with B₁₂ deficiency present differently on clinical exam, (2) whether patients with B₁₂ deficiency and DCM have suboptimal surgical outcomes, (3) whether patients with deficiency who are supplemented with B₁₂ achieve optimal outcomes, and (4) whether increasing B₁₂ levels in patients with no deficiency improves surgical outcomes more than otherwise expected. Since preoperative assessment includes routine blood work, this additional diagnostic measurement would not unnecessarily burden the patient or substantially increase costs. In the event that a patient appears to have suboptimal levels or deficiency, treatment with B₁₂ would not be costly, is unlikely to adversely affect the patient, and may optimize surgical outcome. Further studies in this area are needed and would be highly feasible given the fact that B₁₂ is an essential vitamin, cheap, and readily accessible. We intend to investigate this relationship and will seek to report on how to incorporate B₁₂ assessment into the clinical management of patients with DCM.


Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Sciubba is a consultant for Medtronic, Depuy-Synthes, Stryker, Nuvasive, and K2M. The other authors have no conflicts of interest to declare.

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