

# Clinical Presentation of Subacute Combined Degeneration in a Patient With Chronic B12 Deficiency

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**Background:** Subacute combined degeneration (SCD) is a rare complication of chronic vitamin B12 deficiency that presents with a variety of neurologic findings, including decreased sensation in the extremities, increased falls, and visual changes. Treatment of SCD involves prompt replacement of vitamin B12 and addressing the underlying conditions that cause the deficiency. Given the prevalence of B12 deficiency in the older adult population, clinicians should remain alert to its possibility in patients who present with progressive neuropathy.

**Case Presentation:** This report presents a case of a patient with progressive SCD secondary to chronic B12 deficiency despite monthly intramuscular B12 injections.

**Conclusions:** Appropriate B12 replacement is aggressive and involves intramuscular B12 1000 mcg every other day for 2 to 3 weeks, followed by additional IM administration every 2 months before transitioning to oral therapy. Failure to adequately replenish B12 can lead to progression or lack of resolution of SCD symptoms.

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Subacute combined degeneration (SCD) is an acquired neurologic complication of vitamin B12 (cobalamin) or, rarely, vitamin B9 (folate) deficiency. SCD is characterized by progressive demyelination of the dorsal and lateral spinal cord, resulting in peripheral neuropathy; gait ataxia; impaired proprioception, vibration, and fine touch; optic neuropathy; and cognitive impairment.<sup>1</sup> In addition to SCD, other neurologic manifestations of B12 deficiency include dementia, depression, visual symptoms due to optic atrophy, and behavioral changes.<sup>2</sup> The prevalence of SCD in the US has not been well documented, but B12 deficiency is reported at 6% in those aged < 60 years and 20% in those > 60 years.<sup>3</sup>

Causes of B12 and B9 deficiency include advanced age, low nutritional intake (eg, vegan diet), impaired absorption (eg, inflammatory bowel disease, autoimmune pernicious anemia, gastrectomy, pancreatic disease), alcohol use, tapeworm infection, medications, and high metabolic states.<sup>2,4</sup> Impaired B12 absorption is common in patients taking medications, such as metformin and proton pump inhibitors (PPI), due to suppression of ileal membrane transport and intrinsic factor activity.<sup>5-7</sup> B-vitamin deficiency can be exacerbated by states of increased cellular turnover, such as polycythemia vera, due to elevated DNA synthesis.

Patients may experience permanent neurologic damage when the diagnosis and treat-

ment of SCD are missed or delayed. Early diagnosis of SCD can be challenging due to lack of specific hematologic markers. In addition, many other conditions such as diabetic neuropathy, malnutrition, toxic neuropathy, sarcoidosis, HIV, multiple sclerosis, polycythemia vera, and iron deficiency anemia have similar presentations and clinical findings.<sup>8</sup> Anemia and/or macrocytosis are not specific to B12 deficiency.<sup>4</sup> In addition, patients with B12 deficiency may have a normal complete blood count (CBC); those with concomitant iron deficiency may have minimal or no mean corpuscular volume (MCV) elevation.<sup>4</sup> In patients suspected to have B12 deficiency based on clinical presentation or laboratory findings of macrocytosis, serum methylmalonic acid (MMA) can serve as a direct measure of B12 activity, with levels > 0.75  $\mu\text{mol/L}$  almost always indicating cobalamin deficiency.<sup>9</sup> On the other hand, plasma total homocysteine (tHcy) is a sensitive marker for B12 deficiency. The active form of B12, holotranscobalamin, has also emerged as a specific measure of B12 deficiency.<sup>9</sup> However, in patients with SCD, measurement of these markers may be unnecessary due to the severity of their clinical symptoms.

The diagnosis of SCD is further complicated because not all individuals who develop B12 or B9 deficiency will develop SCD. It is difficult to determine which patients will develop SCD because the minimum level of serum B12 required for

normal function is unknown, and recent studies indicate that SCD may occur even at low-normal B12 and B9 levels.<sup>2,4,10</sup> Commonly, a serum B12 level of < 200 pg/mL is considered deficient, while a level between 200 and 300 pg/mL is considered borderline.<sup>4</sup> The goal level of serum B12 is > 300 pg/mL, which is considered normal.<sup>4</sup> While serologic findings of B-vitamin deficiency are only moderately specific, radiographic findings are highly sensitive and specific for SCD. According to Briani and colleagues, the most consistent finding in SCD on magnetic resonance imaging (MRI) is a “symmetrical, abnormally increased T2 signal intensity, commonly confined to posterior or posterior and lateral columns in the cervical and thoracic spinal cord.”<sup>2</sup>

We present a case of SCD in a patient with low-normal vitamin B12 levels who presented with progressive sensorimotor deficits and vision loss. The patient was subsequently diagnosed with SCD by radiologic workup. His course was complicated by worsening neurologic deficits despite B12 replacement. The progression of his clinical symptoms demonstrates the need for prompt, aggressive B12 replacement in patients diagnosed with SCD.

### CASE PRESENTATION

A 63-year-old man presented for neurologic evaluation of progressive gait disturbance, paresthesia, blurred vision, and increasing falls despite use of a walker. Pertinent medical history included polycythemia vera requiring phlebotomy for approximately 9 years, alcohol use disorder (18 servings weekly), type 2 diabetes mellitus, and a remote episode of transient ischemic attack (TIA). The patient reported a 5-year history of burning pain in all extremities. A prior physician diagnosis attributed the symptoms to polyneuropathy secondary to iron deficiency anemia in the setting of chronic phlebotomy for polycythemia vera and high erythropoiesis. He was prescribed gabapentin 600 mg 3 times daily

**TABLE 1** Examinations on First Presentation for Bilateral Upper and Lower Extremities

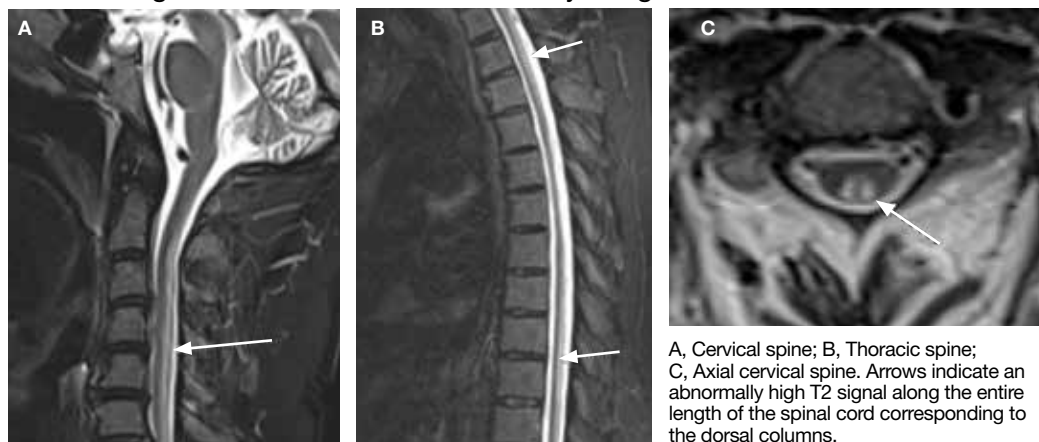
Examination Types	Actions
<b>Physical</b>	
Cardiac	Regular rate and rhythm; no murmurs, gallops, rubs, S3, or S4
Pulmonary	Clear to auscultation bilaterally; no wheezes or rales
Abdomen	Soft, nontender, nondistended, positive bowel sounds on auscultation
Extremities	No edema, pulses equal and palpable
<b>Neurologic</b>	
Deep tendon reflexes	Upper extremities: biceps brachii, triceps, brachioradialis: 1+
Light touch	Lower extremities: patellar and Achilles: absent
Pinprick	Babinski and Hoffman negative
Pain	Reduced in BUE and minimal in BLE
Vibration	Absent in BLE up to the mid-thighs and intact in distal BUE
Temperature	Intact in BUE and BLE
Proprioception	Absent in BLE to hip, mildly reduced in BUE
Finger to nose	Absent in BLE up to the hips, intact in BUE
Heel to shin	Absent in bilateral toes and ankles, intact in BUE, positive Romberg
Rapid alternating movements	Unremarkable
Gait	Unable to perform due to weakness; mild dysidiadochokinesia of left hand; wide-based, unsteady, antalgic gait with ankles externally rotated bilaterally

Abbreviations: BLE, bilateral lower extremities; BUE, bilateral upper extremities.

for pain control. B12 deficiency was considered an unlikely etiology due to a low-normal serum level of 305 pg/mL (reference range, 190-950 pg/mL) and normocytosis, with MCV of 88 fL (reference range, 80-100 fL). The patient also reported a 3-year history of blurred vision, which was initially attributed to be secondary to diabetic retinopathy. One week prior to presenting to our clinic, he was evaluated by ophthalmology for new-onset, bilateral central visual field defects, and he was diagnosed with nutritional optic neuropathy.

Ophthalmology suspected B12 deficiency. Notable findings included reduced deep tendon reflexes (DTRs) in the upper extremities and absent DTRs in the lower extremities, reduced sensation to light touch in all extremities, absent sensation to pinprick, vibration, and temperature in the lower extremities, positive Romberg sign, and a wide-based antalgic gait with the ankles externally rotated bilaterally (Table 1).

Previous cardiac evaluation failed to provide a diagnosis for syncopal episodes. MRI of the brain revealed non-specific white matter changes consistent with chronic microvascular ischemic disease.

**FIGURE** Sagittal Short  $T_2$  Inversion Recovery Images

Electromyography was limited due to pain but showed severe peripheral neuropathy. Laboratory results showed megalocytosis, low-normal serum B12 levels, and low serum folate levels (Table 2). The patient was diagnosed with polyneuropathy and was given intramuscular (IM) vitamin B12 1000 mcg once and a daily multivitamin (containing 25 mcg of B12). He was counseled on alcohol abstinence and medication adherence and was scheduled for follow-up in 3 months. He continued outpatient phlebotomy every 6 weeks for polycythemia.

At 3-month follow-up, the patient reported medication adherence, continued alcohol use, and worsening of symptoms. Falls, which now occurred 2 to 3 times weekly despite proper use of a walker, were described as sudden loss of bilateral lower extremity strength without loss of consciousness, palpitations, or other prodrome. Laboratory results showed minimal changes. Physical examination of the patient demonstrated similar deficits as on initial presentation. The patient received one additional B12 1000 mcg IM. Gabapentin was replaced with pregabalin 75 mg twice daily due to persistent uncontrolled pain and paresthesia. The patient was scheduled for a 3-month follow-up (6 months from initial visit) and repeat serology.

At 6-month follow-up, the patient showed continued progression of disease with significant difficulty using the walker, worsening falls, and wheelchair use required. Physical examination showed de-

creased sensation bilaterally up to the knees, absent bilateral patellar and Achilles reflexes, and unsteady gait. Laboratory results showed persistent subclinical B12 deficiency. MRI of the brain and spine showed high T2 signaling in a pattern highly specific for SCD. A formal diagnosis of SCD was made. The patient received an additional B12 1000 mcg IM once. Follow-up phone call with the patient 1 month later revealed no progression or improvement of symptoms.

### Radiographic Findings

MRI of the cervical and thoracic spine demonstrated abnormal high T2 signal starting from C2 and extending along the course of the cervical and thoracic spinal cord (Figure). MRI in SCD classically shows symmetric, bilateral high T2 signal within the dorsal columns; on axial images, there is typically an inverted "V" sign.<sup>2,4</sup> There can also be abnormal cerebral white matter change; however, MRI of the brain in this patient did not show any abnormalities.<sup>2</sup> The imaging differential for this appearance includes other metabolic deficiencies/toxicities: copper deficiency; vitamin E deficiency; methotrexate-induced myelopathy, and infectious causes: HIV vacuolar myelopathy; and neurosyphilis (tabes dorsalis).<sup>4</sup>

### DISCUSSION

This case demonstrates the clinical and radiographic findings of SCD and underscores the need for high-intensity dosing of B12 replacement in patients with SCD to prevent

progression of the disease and development of morbidities.

Symptoms of SCD may manifest even when the vitamin levels are in low-normal levels. Its presentation is often nonspecific, thus radiologic workup is beneficial to elucidate the clinical picture. We support the use of spinal MRI in patients with clinical suspicion of SCD to help rule out other causes of myelopathy. However, an MRI is not indicated in all patients with B12 deficiency, especially those without myelopathic symptoms. Additionally, follow-up spinal MRIs are useful in monitoring the progression or improvement of SCD after B12 replacement.<sup>2</sup> It is important to note that the MRI findings in SCD are not specific to B12 deficiency; other causes may present with similar radiographic findings.<sup>4</sup> Therefore, radiologic findings must be correlated with a patient's clinical presentation.

B12 replacement improves and may resolve clinical symptoms and abnormal radiographic findings of SCD. The treatment duration of B12 deficiency depends on the underlying etiology. Reversible causes, such as metformin use > 4 months, PPI use > 12 months, and dietary deficiency, require treatment until appropriate levels are reached and symptoms are resolved.<sup>4,11</sup> The need for chronic metformin and PPI use should also be reassessed regularly. In patients who require long-term metformin use, IM administration of B12 1000 mcg annually should be considered, which will ensure adequate storage for more than 1 year.<sup>12,13</sup> In patients who require long-term PPI use, the risk and benefits of continued use should be measured, and if needed, the lowest possible effective PPI dose is recommended.<sup>14</sup> Irreversible causes of B12 deficiency, such as advanced age, prior gastrectomy, chronic pancreatitis, or autoimmune pernicious anemia, require lifelong supplementation of B12.<sup>4,11</sup>

In general, oral vitamin B12 replacement at 1000 to 2000 mcg daily may be as effective as parenteral replacement in patients with mild to moderate deficiency or neurologic symptoms.<sup>11</sup> On the other hand, patients with SCD often require parenteral replacement of B12 due to the severity of their deficiency or neurologic symptoms, need for more rapid improvement in symptoms, and prevention of irreversible neurological deficits.<sup>4,11</sup> Appropriate B12 replacement in SCD

**TABLE 2** Laboratory Results at Initial Neurologic Visit

Tests	Initial Visit	3 mo Follow-up	Reference Ranges
Folate, nmol/L	10.1	5.2 <sup>a</sup>	6.1-38.5
B12, pg/mL	192	412	190-950
Red blood cell, $\times 10^6/\mu\text{m}$	4.9	5.20	4.5-5.9 <sup>b</sup>
Hemoglobin, g/dL	18.3 <sup>c</sup>	18.0	14.0-17.5 <sup>b</sup>
Hematrit, %	50.7 <sup>c</sup>	53.5 <sup>c</sup>	41.5-50.4 <sup>b</sup>
MCV, fL	104.3 <sup>c</sup>	102.9 <sup>c</sup>	80-100
MCH, pg	37.7 <sup>c</sup>	34.6 <sup>c</sup>	27.5-33.2
MCHC, g/dL	36.1 <sup>c</sup>	33.6 <sup>c</sup>	33.4-35.5 <sup>c</sup>
Platelet, $\times 10^3/\mu\text{m}$	203	231	150-450
RDW, %	55.4 <sup>c</sup>	52.4 <sup>c</sup>	11.8-14.5 <sup>b</sup>
Mean platelet volume, fL	10.9	10.7	7-12

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width.

<sup>a</sup>Low level.

<sup>b</sup>Reference range for men.

<sup>c</sup>Elevated level.

requires intensive initial therapy which may involve IM B12 1000 mcg every other day for 2 weeks and additional IM supplementation every 2 to 3 months afterward until resolution of deficiency.<sup>4,14</sup> IM replacement may also be considered in patients who are nonadherent to oral replacement or have an underlying gastrointestinal condition that impairs enteral absorption.<sup>4,11</sup>

B12 deficiency is frequently undertreated and can lead to progression of disease with significant morbidity. The need for high-intensity dosing of B12 replacement is crucial in patients with SCD. Failure to respond to treatment, as shown from the lack of improvement of serum markers or symptoms, likely suggests undertreatment, treatment nonadherence, iron deficiency anemia, an unidentified malabsorption syndrome, or other diagnoses. In our case, significant undertreatment, compounded by his suspected iron deficiency anemia secondary to his polycythemia vera and chronic phlebotomies, are the most likely etiologies for his lack of clinical improvement.

Multiple factors may affect the prognosis of SCD. Males aged < 50 years with absence of anemia, spinal cord atrophy, Romberg

sign, Babinski sign, or sensory deficits on examination have increased likelihood of eventual recovery of signs and symptoms of SCD; those with less spinal cord involvement (< 7 cord segments), contrast enhancement, and spinal cord edema also have improved outcomes.<sup>4,15</sup>

## CONCLUSIONS

SCD is a rare but serious complication of chronic vitamin B12 deficiency that presents with a variety of neurological findings and may be easily confused with other illnesses. The condition is easily overlooked or misdiagnosed; thus, it is crucial to differentiate B12 deficiency from other common causes of neurologic symptoms. Specific findings on MRI are useful to support the clinical diagnosis of SCD and guide clinical decisions. Given the prevalence of B12 deficiency in the older adult population, clinicians should remain alert to the possibility of these conditions in patients who present with progressive neuropathy. Once a patient is diagnosed with SCD secondary to a B12 deficiency, appropriate B12 replacement is critical. Appropriate B12 replacement is aggressive and involves IM B12 1000 mcg every other day for 2 to 3 weeks, followed by additional IM administration every 2 months before transitioning to oral therapy. As seen in this case, failure to adequately replenish B12 can lead to progression or lack of resolution of SCD symptoms.

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## Disclaimer

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## Ethics and consent

No identifying patient information was discussed in the case report.

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