

Pearls & Oysters: Late-Onset Cobalamin C Deficiency Presenting With Subacute Combined Degeneration

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Abstract

Cobalamin C (CblC) deficiency is a rare inborn error in cobalamin (vitamin B12) metabolism which results in impaired intracellular processing of dietary vitamin B12. This leads to a wide range of clinical manifestations including cognitive impairment, psychiatric symptoms, myelopathy, thrombotic events, glomerulonephritis, and pulmonary arterial hypertension. CblC deficiency typically presents in the pediatric population but can also present in adulthood. Diagnosis in adults can be challenging due to the rarity of this condition and its myriad clinical presentations. CblC deficiency is treatable, so early diagnosis is important in preventing permanent neurologic damage. Although CblC deficiency results from a defect in vitamin B12 metabolism, B12 levels remain normal. Diagnosis depends on testing metabolites altered by vitamin B12 dysfunction such as methylmalonic acid (MMA) and homocysteine. We presented a case of a 20-year-old woman who presented with chronic progressive lower extremity weakness and sensory changes. She was eventually diagnosed with subacute combined degeneration because of CblC deficiency and effectively treated. This case highlights the importance of considering inborn errors of metabolism in adult patients and including testing of metabolites such as MMA and homocysteine when suspecting vitamin B12 dysfunction.

Pearls

- Cobalamin C (CblC) deficiency is a rare cause of myelopathy in adults.
- CblC deficiency can present with a range of neurologic, psychiatric, and systemic symptoms.
- CblC deficiency is treatable, and early diagnosis can help prevent permanent neurologic damage.

Oysters

- Testing solely for vitamin B12 without methylmalonic acid (MMA) and homocysteine will miss inborn errors in metabolism such as CblC deficiency.

Case Report

A previously healthy 20-year-old woman presented with nine months of gradually progressive lower extremity weakness and numbness. Her symptoms began insidiously with mild leg weakness manifesting as intermittent knee buckling and difficulty getting up from chairs. Several months later, she developed lower extremity numbness and paresthesias. Her weakness gradually progressed until she was unable to ambulate without assistance. Throughout this course, she denied upper extremity symptoms, cognitive changes, psychiatric symptoms, vision problems, blood clots, or bladder/bowel dysfunction. There was no identifiable illness, vaccination, or physiologic stressors before symptom onset. She denied dietary restrictions (e.g., veganism) or recreational drug use including nitrous oxide. There was no family history of consanguinity or neurologic disorders. She was up to date on vaccinations, and her newborn screen was normal at birth.

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She was initially seen by a neurologist. At that time, her examination revealed normal cognition, intact cranial nerves, normal fundi, and normal upper extremity strength. Her lower extremities were diffusely weak with 4/5 strength throughout. Upper extremity reflexes were normal, and there was areflexia at the patella and clonus at the ankles bilaterally. Her sensory examination demonstrated decreased vibratory sensation and proprioception in her legs bilaterally. Temperature and pinprick sensation were spared. Gait was wide-based, and she required a walker for ambulation. MRI of the cervical and thoracic spine demonstrated longitudinally extensive T2 hyperintensities involving the dorsal columns extending from C5 to T11 (Figure 1). EMG showed active denervation in multiple myotomes. Her MRI of the brain (Figure 2) and laboratory workup were unremarkable, including normal vitamin B12 (625 pg/mL, reference range 232–1,245 pg/mL), negative aquaporin 4 (AQP4 Ab), and negative myelin oligodendrocyte glycoprotein (anti MOG Ab) antibodies. MMA and homocysteine were not tested at this time.

She was referred to a tertiary care center for further evaluation. Lumbar puncture was performed which revealed a normal CSF profile, negative oligoclonal bands, and negative meningoencephalitis panel. Serum studies for infectious pathogens were negative, including HIV, HTLV1/II, syphilis, and tuberculosis. Rheumatologic studies were normal, including CRP, ESR, ANA, ANCA, RF, SSA, and SSB. Initial nutritional studies were unremarkable, including vitamin B12 (765 pg/mL), folate, copper, and alpha tocopherol. However, MMA and total homocysteine eventually returned elevated at 85.23 umol/L (reference range 0.0–0.40 umol/L) and 165 umol/L (reference range 0–14 umol/L), respectively. This raised suspicion for an inborn error in metabolism, so the patient was empirically started on treatment for CblC deficiency with hydroxocobalamin 5 mg IM daily, betaine 1 g 3 times daily, folinic acid 15 mg twice daily, and levocarnitine 660 mg 3 times daily. Genetic testing confirmed compound heterozygous variations in the *MMACHC* gene, c271dupA (pathologic) and c449T>A (variant of unknown significance). Her

parents received genetic testing, which confirmed that each carried 1 mutant allele. She was diagnosed with subacute combined degeneration because of CblC deficiency. On follow-up 5 months after initiating treatment, she was fully ambulatory with only trace hip flexor weakness and mild loss of vibratory sensation bilaterally.

Discussion

CblC deficiency is an inborn error in vitamin B12 metabolism that can present with a wide range of neurologic symptoms including myelopathy. While the condition is rare, it is important to recognize because it is readily treatable. This case illustrates the importance of considering inborn errors in metabolism, such as CblC deficiency, in adults and including MMA and homocysteine as part of the evaluation when vitamin B12 deficiency is suspected.

CblC deficiency, also known as combined methylmalonic acidemia and homocystinuria (CblC type), is a rare inborn error in cobalamin (vitamin B12) metabolism caused by an autosomal recessive variation in the *MMACHC* gene on chromosome 1p34.1.¹ The gene product, *MMACHC* (CblC), acts as a molecular chaperone and catalyzes the reduction of dietary B12 into a form that can be used to synthesize functional coenzymes.¹ A defect in *MMACHC* leads to impaired intracellular conversion of dietary B12 into adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl). Absence of these cofactors leads to impaired enzymatic function of methylmalonyl CoA mutase and methionine synthase, which participate in methylmalonic acid (MMA) degradation and remethylation of homocysteine to methionine, respectively.² This leads to increased levels of MMA and homocysteine, decreased levels of methionine, and subsequent systemic dysfunction.¹

Over 90% of patients with CblC deficiency present in infancy with failure to thrive, developmental delay, hypotonia, and seizures.² Some patients present outside of infancy (>12

Figure 1 Axial T2 MRI Demonstrating Hyperintensity in the Dorsal Columns (A) and Sagittal STIR MRI Demonstrating Longitudinal Extension of the Lesion (B)

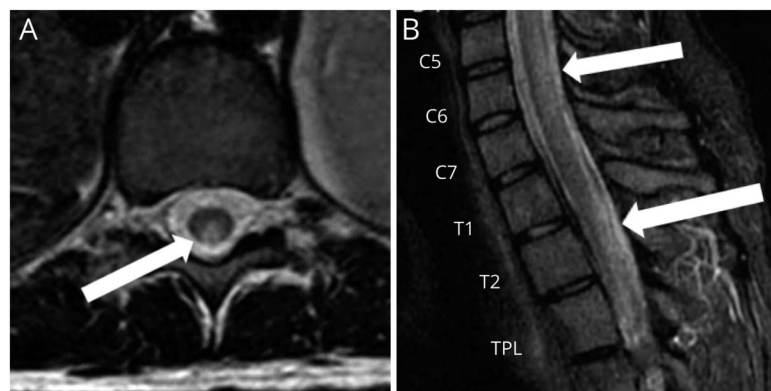
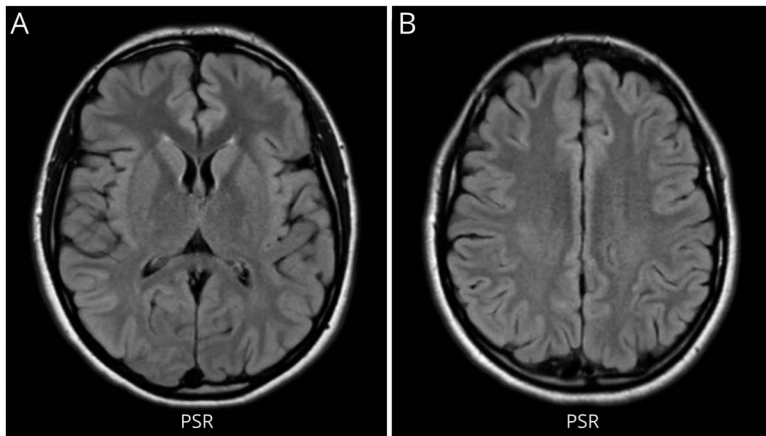


Figure 2 Axial FLAIR MRI Demonstrating Normal Volume and Architecture (A and B)



months) and are referred to as having late-onset CblC deficiency.² These patients can present in adulthood with a wide range of manifestations including cognitive impairment, psychiatric symptoms, myelopathy, thrombotic events, glomerulonephritis, and pulmonary arterial hypertension.²⁻⁴ The disease severity and age at onset depend on the underlying *MMACHC* variation. However, clinical presentation in late-onset disease is highly variable within the same variation.³ The variations c271dupA and c331C>T are associated with more severe, early onset disease in the homozygous or compound heterozygous state.⁵ Late-onset disease is associated with the variations c394C>T and c482G>A, which manifest with late-onset disease even in the compound heterozygous state with a more deleterious variation such as c271dupA.^{5,6} Multiple other less common variations have also been described but are outside the scope of this article.⁵ Our patient was compound heterozygous for c271dupA and a second previously undescribed variation, c449T>A (pIle150Lys). This latter variation encodes for a charged amino acid (lysine) in place of a nonpolar amino acid (isoleucine). This is a significant change in amino acid character which could alter protein function. Because CblC is an autosomal recessive disorder, it can be inferred that the variation c449T>A is pathologic and corresponds to a late-onset phenotype given our patient's late presentation in a compound heterozygous state with c271dupA.

CblC deficiency has been part of the newborn screen in the United States since the early 2000s and was introduced in California in 2005.^{7,8} Based on our patient's age, she would not have been screened at birth. Newborn screening has aided in the early detection and treatment of many individuals with this condition.⁷ Early treatment improves survival and prevents many serious complications such as hemolytic uremic syndrome and hematologic abnormalities. However, individuals with early onset disease tend to develop cognitive impairment and vision loss regardless of treatment.⁵ Late-onset cases tend to do better and can have complete resolution of

deficits with treatment.⁵ Despite the success of newborn screening, it is unclear whether current screening methods are sensitive for milder forms of CblC deficiency because there are several reports of cases missed by the newborn screen.^{6,9}

Myelopathy is a common presentation of late-onset CblC deficiency. Huemer et al. identified myelopathy in 12 of 58 of their cases, and Wang et al. identified myelopathy in all 16 of their cases.^{2,3} Our patient presented with isolated subacute combined degeneration and peripheral neuropathy. Initially, vitamin B12 deficiency was suspected given the history and imaging findings. However, during the initial encounter, vitamin B12 was checked in isolation without MMA or homocysteine. This led to the premature conclusion that vitamin B12 dysfunction was not present and ultimately delayed diagnosis. Dysfunction in B12 metabolism was only identified after MMA and homocysteine were checked. This illustrates the importance of including CblC deficiency in the differential of myelopathy and testing for MMA and homocysteine when vitamin B12 deficiency is suspected.

Our patient was treated with hydroxocobalamin, betaine, and folic acid with improvement in her symptoms. Current guidelines recommend starting parenteral hydroxocobalamin and oral betaine as soon as there is suspicion of CblC deficiency.^{1,5} Hydroxocobalamin is given intramuscularly (IM) at a starting dose of either 1 mg or 0.3 mg/kg daily.^{1,5} The formulation is important since parenteral hydroxocobalamin has been shown to be more effective than oral cyanocobalamin.^{1,5} Betaine is started orally at 250 mg/kg/d divided thrice daily.^{1,5} Both hydroxocobalamin and betaine have clinically proven efficacy. Folic acid, methionine, and L carnitine lack strong evidence and are recommended on theoretical principles.^{1,5} Treatment is adjusted to target vitamin B12 levels above 1,000,000 pg/mL, normalization of methionine, and reduction in MMA and total homocysteine.¹ There are limited guidelines for long-term surveillance, but it is common to monitor vitamin B12, MMA, total homocysteine, renal function, and

hematologic parameters.⁵ All patients with CblC deficiency should be seen by an ophthalmologist at the time of diagnosis regardless of symptoms.⁵ Patients should be counseled to avoid protein restriction and nitrous oxide exposure, such as with dental anesthesia.⁵ Outcomes are variable, ranging from complete recovery to death, and depend in part on the genetic profile and duration of untreated disease. Patients with late-onset disease tend to do better and can have significant improvement if treated early.^{1,5}

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Name	Location	Contribution
Christopher Goyne, MD	University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content

Appendix (continued)

Name	Location	Contribution
Leena Kansal, MD	University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content

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