

A Treatable Metabolic Cause of Encephalopathy: Cobalamin C Deficiency in an 8-Year-Old Male

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abstract

Neurologic regression in a previously healthy child may be caused by metabolic or neurodegenerative disorders, many of which have no definitive treatment. We report a case of a previously healthy 8-year-old boy who presented with a month-long history of waxing and waning encephalopathy and acute regression, followed by seizures. Evaluation for a metabolic disorder revealed methylmalonic acidemia and hyperhomocysteinemia of the cobalamin C type due to a single, presumed homozygous pathogenic c.394 C>T mutation in the *MMACHC* gene. With the appropriate diet restrictions and vitamin replacement, he improved significantly and returned to his premorbid level of behavior. This case illustrates an unusual presentation of a treatable metabolic disorder and highlights the need to consider cobalamin defects in the differential diagnosis of healthy children with neurologic regression.

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Reversible causes of metabolic or neurodegenerative disorders in children are rare. Here we present a case of a treatable inborn error of metabolism, cobalamin C deficiency (cblC), presenting as the subacute onset of cognitive regression, hallucinations, and seizures in a previously healthy 8-year-old boy with consanguineous parents. Symptoms reversed with treatment of the primary metabolic defect.

Disorders of intracellular cobalamin metabolism cause elevations in methylmalonic acid (MMA), homocysteine, or both. The biochemical phenotypes comprise complementation groups, which are defined by somatic cell analysis. The disorders are referred to by the prefix "cbl" followed by the capital letter specifying the complementation group. Elevation of MMA and homocysteine due to a disorder of cbl metabolism is most commonly caused by a mutation in the gene *MMACHC*.¹

The most common disorder of cobalamin metabolism is cblC. Early

onset of the deficiency can occur in utero, in infants, or in toddlers, and is characterized by a combination of failure to thrive, feeding difficulties, and neurologic symptoms. Late-onset deficiency presents in adolescents and adults and is typically characterized by neurologic and cognitive symptoms, including encephalopathy and seizures.² Our case is an example of a child presenting at a young age but with the neurologic deficits characteristic of late-onset deficiency. This case highlights the extensive differential diagnosis of encephalopathy in healthy children and the importance of testing for treatable causes of metabolic disorders when evaluating a child with these symptoms. The presence of consanguinity underscores the necessity for obtaining a thorough family history. Such a history increases the probability of a genetically determined metabolic disease, which may reduce the time required to establish a diagnosis and to provide therapy.

PATIENT PRESENTATION

An 8-year-old previously healthy, normally developed boy born to consanguineous (first cousins) parents presented to the emergency department (ED) with a 1-month history of mental status changes. His symptoms began with the inability to answer simple questions and progressed to an inability to follow commands or complete simple tasks (for example, brush his teeth). He developed hesitant speech with difficulties articulating, then an absence of spontaneous speech. He began to sleep for only 2 to 3 hours at night. He was emotionally labile and did not make eye contact. Two weeks before admission, he had been evaluated by a psychiatrist and treated with fluoxetine. He was the product of a normal pregnancy and birth, and his newborn screen was reported as normal to his pediatrician. Specific values tested were not provided in the initial report. In 2004, the Illinois Department of Public Health Neonatal Screen tested for hypothyroidism; galactosemia; biotinidase deficiency; congenital adrenal hyperplasia; sickle cell disease; and amino acid, fatty acid oxidation, and organic acid diseases.³ Family history was unremarkable.

Vital signs and general physical examination in the ED were normal. The patient was abulic and had no spontaneous speech. He could answer some simple questions but had difficulty following simple commands. He had spontaneous inappropriate outbursts of laughter and crying. The remainder of the neurologic examination was normal with no focal findings.

Initial serum and cerebral spinal fluid studies for infectious (complete blood count, erythrocyte sedimentation rate, C-reactive protein), autoimmune (thyroid function tests, antithyroid antibodies, antinuclear antibody, antibodies to double-stranded DNA, antineutrophil cytoplasmic antibodies, and paraneoplastic

antibodies, including N-methyl-D-aspartate antibodies), toxins, or metabolic (comprehensive metabolic panel; iron, folate, and copper serum levels) disorders were found to be within normal limits. Ammonia was slightly elevated, likely an artifact of the method of collection and not felt to be indicative of disease. Total folate was increased, possibly secondary to a methyl-folate trap from a dysfunctional cobalamin pathway.⁴ MRI of the brain showed mild to moderate volume loss. Routine EEG showed a slow dominant posterior rhythm and marked slow-wave abnormalities over the frontal lobe. The patient's mental status improved briefly after a dose of lorazepam (Ativan) was administered. He was treated with fosphenytoin and then developed agitation with tachycardia, confusion, and episodes of breath-holding. Repeat EEG showed multifocal sharp waves and a slow background for age. Zonisamide was started, which improved his sleep cycle. Delirium continued and he had difficulty sitting and walking without assistance. He was treated with methylprednisolone sodium succinate (Solu-Medrol) for 3 days followed by intravenous immune globulin (1 g/kg per day intravenously for 2 days) for presumed autoimmune encephalopathy before transfer to an inpatient rehabilitation hospital, where his delirium and confusion improved.

Two weeks after discharge, the patient was readmitted in status epilepticus. He had started to experience visual hallucinations 3 days before presentation and zonisamide had been weaned. Evaluation for metabolic causes of cognitive regression in a previously healthy child was initiated. In addition to repeating some of the

previous studies, plasma amino acids, urine organic acids, and acylcarnitine esters were measured to further screen for metabolic disorders. Homocysteine was found to be elevated (6 [normal 0 $\mu\text{M/L}$]), cystathionine was elevated (12 [range 0–3 $\mu\text{M/L}$]), and methionine was low (5 [normal 7–47 $\mu\text{M/L}$]). Total and free carnitine levels were low (9.7 [normal 28–83 $\mu\text{mol/L}$] and 7 [normal 22–66 $\mu\text{mol/L}$]), the acylcarnitine-to-free carnitine ratio was normal (0.4 [normal 0.1–0.9 $\mu\text{mol/L}$]). Propionylcarnitine (C3) was elevated, and the acetylcarnitine was found to be low. Serum MMA and total plasma homocysteine levels were significantly elevated (Table 1). Urine organic acids also showed an elevated MMA level. Genetic testing revealed a single copy of a previously identified pathogenic mutation, c.394 C>T, in the *MMACHC* gene, suggesting a diagnosis of a cblC deficiency. Homozygosity was presumed secondary to a history of consanguinity, but was not confirmed by parental testing. A retrospective review of the patient's newborn blood spot revealed a C3 concentration of 8.49 $\mu\text{M/L}$ (normal 0.0100–8.00), which was not flagged as abnormal by the laboratory. The patient was evaluated formally by ophthalmology and found to have no ocular abnormalities.

The patient's brother was also subsequently tested and found to have the same biochemical derangements. His newborn screening was remarkable for a C3 of 6.77 $\mu\text{M/L}$ (normal 0.0100–8.00). The brother's clinical course was much milder and his examination was remarkable only for subtle spasticity. The patient's brother was not evaluated formally by ophthalmology, but his bedside examination was unremarkable.

TABLE 1 Homocysteine and Methylmalonic Acid Levels, at Diagnosis and After Treatment

Compound [Normal Range]	Diagnosis	3-mo Follow-up	5-mo Follow-up
Homocysteine (serum) [1.2–9.6 $\mu\text{mol/L}$]	109	29.7	48.8
Methylmalonic acid (serum) [87–318 nmol/L]	35 680	1637	741

Treatment was started and included 1 mg (0.03 mg/kg) hydroxycobalamin daily, (which was then transitioned to a maintenance schedule of 5 mg [0.15 mg/kg] injections 3 times a week), 17 mL (50 mg/kg) carnitine twice daily, 7.5 g (220 mg/kg) betaine twice daily, and a low-protein diet following the treatment recommendations for treatment of disorders of cobalamin metabolism.² Over the next 5 months, there was a significant reduction in MMA and homocysteine levels in response to this therapy (Table 1). The slight increase in homocysteine between the third and fifth month of follow-up was ascribed to deviation from the treatment regimen caused by lack of access to the prescribed supplements. The patient continued to have episodes of disorientation and nonsensical speech after initiation of treatment. He had difficulties walking and was discharged to an inpatient rehabilitation facility. Two months after beginning treatment his mental status had returned to his baseline level of functioning, psychiatric symptoms had resolved, and gait improved. The patient's biochemical markers also improved (Table 1).

DISCUSSION

Two phenotypes have been described in cblC disease, depending on the age of presentation.^{2,5} Early-onset deficiency includes in utero changes and symptom onset in infants or toddlers. In utero complications of cblC include microcephaly and restricted growth. Signs and symptoms in newborns and infants are varied and include poor feeding, failure to thrive, and neurologic symptoms, including seizures and infantile spasms.² Rare cases of hemolytic uremic syndrome and hyperammonemia have been reported.⁶ Toddlers also may present with failure to thrive or poor head growth. Global developmental delay can be evident by this age or the patients may present with encephalopathy or hypotonia.^{2,7,8}

Classification by age of onset into an early and late phenotype is imprecise, and some cases of late-onset cblC disease may have had earlier symptoms that went unrecognized.⁹

Late-onset cblC is often thought to occur in otherwise previously healthy adolescents and adults, presenting with neurologic, cognitive, and psychiatric symptoms.^{10,11} The c.394 C>T mutation present in our patient was most commonly associated with late-onset disease (>4 years of age) in a study of 118 patients with cblC disease.⁹ In a case series of 50 patients, Rosenblatt et al⁵ identified 6 patients with onset after the age of 4 years. These patients presented with developmental delay, hypotonia, seizures, dementia, and/or myelopathy. Although cblC is commonly defined by the age of presentation, our case also illustrates the diversity

of symptoms at any age (Table 2). Although not as common, adolescents and older children have been described with late-onset-type symptoms. Shinnar and Singer¹² first reported an early presentation of late-onset deficiency in 1984, in a case of declining school performance, progressive dementia, and myelopathy in a 14-year-old girl. Ben-Omran and colleagues¹¹ described a 10-year-old with acute dementia and catatonic psychotic behavior. Frattini et al¹³ also identified a patient who presented at 7 months of age with symptoms expected in early-onset disease and developed a demyelinating neuropathy over the course of her illness.

The relationship between genotype and phenotype or age of onset in cblC disease and for this specific mutation is variable.^{14,15} Insidious psychiatric and neurologic symptoms have been

TABLE 2 Current Case Reports in the Literature Involving Neurologic Presentations of cblC Deficiency in Adolescents and Adults

Authors	Clinical Presentation	Age, y/Gender
Shinnar and Singer (1984) ¹²	Dementia and myelopathy	14/F
Gold et al (1996) ²⁸	Gait changes, urinary incontinence	12/F
	Peripheral neuropathy	31/F
Augoustides-Savvopoulou et al (1999) ²⁹	Dementia	11/F
Bodamer et al (2001) ³⁰	Encephalopathy, subacute myelopathy, motor neuron disease	19/M
Powers et al (2001) ³¹	Subacute myelopathy	32/M
	Dementia, behavior changes	44/M
Roze et al (2003) ³²	Progressive gait disorder	24/F
	Delusions, visual and auditory hallucinations	16/F
Smith et al (2006) ³³	Subacute combined degeneration	15/M
Ben-Omran et al (2007) ¹¹	Dementia, lactic acidosis, peripheral neuropathy; depression, regression, school failure, incontinence, ataxia, lethargy, seizures	14/F
	Acute dementia, anorexia, weight loss, learning disorder and school failure	10/F
Heil et al (2007) ³⁴	Macrocytic anemia, cognitive regression, marfanoid features	13/F
	Developmental delay, behavioral abnormalities	10/M
Tsai et al (2007) ³⁵	Chronic anemia, depression and psychosis, muscle weakness, paraesthesia of the legs, difficulty ambulating, spinal infarct	35/F
Thauvin-Robinet et al (2008) ¹⁰	Dysarthria, dysmetria, myoclonus, tetraparesis	39/F
	Apraxia, ataxia, spasticity, myelopathy	42/M
	Recurrent venous thrombosis	40/M
Wang et al (2012) ³⁶	Lower extremity weakness, hyporeflexia	22/F
	Cognitive impairment, delirium, gait instability, limb rigidity, auditory hallucinations	40/M
	Difficulty walking, incontinence, dysphagia, epilepsy, cognitive impairment	18/F
Backe et al (2013) ³⁷	Ataxic gait, numbness, partial paralysis in lower extremities, cerebral edema	23/M

F, female; M, male.

reported with a c.394 C>T mutation. In 1 case series including 118 patients, the mutation was identified in patients of Asiatic Indian, Middle Eastern, Italian, and Portuguese descent. Other mutations were more commonly seen in patients of European descent.⁹

The differential diagnosis for mental status changes in children includes structural, metabolic, infectious, autoimmune, toxic, and neurodegenerative causes.¹⁶ Inborn errors of metabolism are often overlooked in older children, but should be considered in the first tier of diagnosis, particularly when the family history is contributory or when parents are consanguineous. As our case also illustrates, metabolic disorders can cause acute or subacute symptoms after a period of normal development. Screening chemistries, hematologic studies, and microbiological tests can help to guide the evaluation.¹⁶ The yield of additional tests, including ammonia, lactate, pyruvate, urine and plasma amino acids, fatty acid, and carnitine profiles and various vitamin levels, depends on the clinical context.¹⁷ Autoimmune causes can be evaluated by testing for individual antibodies, including antithyroid or paraneoplastic antibodies. Thus, the diagnosis of cblC deficiency disorder requires a high index of suspicion, as patients can present with no detectable metabolic or laboratory derangements.¹⁸ The neuropsychiatric and cognitive symptoms can mimic those of an autoimmune disorder, particularly N-methyl-D-aspartate encephalitis.^{19–21} Indeed, our patient was first evaluated by a psychiatrist and treated with fluoxetine before presenting to the ED.

The diagnosis of cobalamin-processing disorders is suggested by amino acid and organic acid measurements that reveal increased concentrations of MMA and homocysteine in the blood and urine when the serum B₁₂ levels are normal. The diagnosis is confirmed by cellular and biochemical studies

and/or molecular genetics. In our patient, a metabolic cause was pursued after his clinical condition failed to improve and autoimmune and paraneoplastic studies were negative. Importantly, B₁₂ deficiency should be ruled out first, and considered early in the differential diagnosis of any patients with cognitive regression or psychiatric symptoms and megaloblastic anemia. The diagnosis can be confirmed with genetic testing, but treatment should not be withheld while awaiting these results.^{10,18} Many state newborn screens have recently included cblC deficiency in their screening programs.²² Although this may be a good screening mechanism for the diagnosis of infants, relatively older children may have been born after the expanded newborn screening was established. In addition, cobalamin defects may be missed on mass spectrometry screening. Test results are often based on elevated C3 levels, of which cutoff levels vary.²² Of 10 patients with confirmed cblC in a cohort presented by Weisfeld-Adams et al,²³ the C3 values ranged from 5.77 to 10.42 $\mu\text{M/L}$.

Early diagnosis of cblC is essential because an established treatment regimen exists. The current recommended treatment regimen includes intramuscular injections of hydroxocobalamin every 1 to 3 days, supplementation with betaine (100 mg/kg per day divided twice daily if <3 years of age, 250 mg/kg per day divided twice daily if older), and carnitine (50–100 mg/kg per day). Adherence to a low-protein diet, as well as supplementation with pyridoxine, folate, and methionine are considered in some patients.^{2,24,25} Hydroxocobalamin has been found to be superior to cyanocobalamin.²⁴ Response to treatment is variable and patients require individualized dose escalation or reduction. One patient required up to 20 mg of hydroxocobalamin daily to achieve both clinical and biochemical response.²⁶ Some patients have had continued clinical decline after

initiation of therapy.²⁷ More research is needed to determine if the established treatment regimen is disease modifying, produces clinical changes, and is effective. Our patient made a near-complete neurologic recovery after beginning treatment.

CONCLUSIONS

Cobalamin-processing disorders, including cblC, are difficult to diagnose, requiring a high index of suspicion. Importantly, early diagnosis and treatment may arrest the progression of disease and correct clinical symptoms. This case illustrates an unusual presentation of neurologic symptoms of this disorder in a young child and highlights the need to consider this treatable metabolic disorder in the differential diagnosis of encephalopathy and seizures in previously healthy children.

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