Cobalamin C Deficiency in an Adolescent With Altered Mental Status and Anorexia

AUTHORS: Maria H. Rahmandar, MD,[a] Amanda Bawcom, MSN, RN, CPNP,[b] Mary E. Romano, MD, MPH,[c] and Rizwan Hamid, MD, PhD[b]

[a]Pediatric Residency Training Program, [b]Division of Medical Genetics and Genomic Medicine, and [c]Division of Adolescent and Young Adult Health, Department of Pediatrics, Monroe Carell Jr Children's Hospital at Vanderbilt University, Nashville, Tennessee

KEY WORDS

adolescent, anorexia, ataxia, cobalamin C deficiency, psychotic disorder

ABBREVIATIONS

C3—propionylcarnitine
cbl—cobalamin
IEM—inborn error of metabolism
NBS—newborn screening
PAA—plasma amino acids
UOA—urine organic acids

Dr Rahmandar was a member of the pediatric team caring for the patient, drafted the initial manuscript, and reviewed and revised the manuscript, and approved the final manuscript as submitted; Ms Bawcom is a pediatric metabolic nurse practitioner who was involved in the care of this patient, collected data, and reviewed the manuscript; Dr Romano critically reviewed and revised the manuscript and approved the final manuscript as submitted; and Dr Hamid was the biochemical geneticist who evaluated the patient, helped in diagnosis, wrote sections of the manuscript, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Address correspondence to Maria H. Rahmandar, MD, Adolescent Medicine Fellowship Program, Division of Adolescent and Transition Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 4000, Cincinnati, OH 45229. Email: maria.rahmandar@cchmc.org Rizwan Hamid, MD, PhD, Division of Medical Genetics and Genomic Medicine, Room DD2205, MCN, Vanderbilt University, Nashville, TN 37232. E-mail: rizwan.hamid@vanderbilt.edu

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abstract

Although cobalamin (cbl) C deficiency is the most common inherited disorder of vitamin B_{12} metabolism, the late-onset form of the disease can be difficult to recognize because it has a broad phenotypic spectrum. In this report, we describe an adolescent female exposed to unknown illicit substances and sexual abuse who presented with psychosis, anorexia, seizures, and ataxia. The patient's diagnosis was delayed until a metabolic workup was initiated, revealing hyperhomocysteinemia, low normal plasma methionine, and methylmalonic aciduria. Ultimately, cblC deficiency was confirmed when molecular testing showed compound heterozygosity for mutations (c.271dupA and c.482G>A) in the *MMACHC* gene. This diagnosis led to appropriate treatment with hydroxocobalamin, betaine, and folate, which resulted in improvement of her clinical symptoms and laboratory values. This patient demonstrates a previously unrecognized presentation of late-onset cblC deficiency. Although neuropsychiatric symptoms are common in late-onset disease, seizures and cerebellar involvement are not. Furthermore, anorexia has not been previously described in these patients. This case emphasizes that inborn errors of metabolism should be part of the differential diagnosis for a teenager presenting with altered mental status, especially when the diagnosis is challenging or neurologic symptoms are unexplained. Correct diagnosis of this condition is important because treatment is available and can result in clinical improvement.[1] *Pediatrics* 2014;134:e1709–e1714

Inborn errors of cobalamin (cbl; vitamin B_{12}) metabolism are rare disorders with broad phenotypic presentations, making them both clinically challenging and difficult to diagnose (for an updated review, see Carrillo-Carrasco et al).[2] Cbl undergoes a series of modifications into its active forms: adenosylcobalamin, the cofactor for methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA, and methylcobalamin, the cofactor for methionine synthase, which converts homocysteine to methionine.[3–5] Disorders of cbl metabolism are classified into several complementation classes, some of which (cblC,[6] cblD,[7] cblF,[8] cblJ,[9] and cblX[10] deficiencies) result in dysfunction of both methylmalonyl-CoA mutase and methionine synthase, and subsequent hyperhomocysteinemia and methylmalonic aciduria.[3–5] The most commonly affected complementation class is cblC, the incidence of which is estimated to be 1 in 100 000.[3,11] Approximately 400 patients with cblC deficiency have been described, with only 10% presenting in adolescence or adulthood.[12,13] Late-onset disease can be subtle, with progressive psychosis, cognitive decline, and neurologic abnormalities contributing to an often complicated path to diagnosis. Compared with early-onset, however, late-onset cases are more likely to have a better prognosis if diagnosed and treated.[5,14,15]

We report a case of an adolescent girl who presented with psychosis and anorexia and later developed seizures and ataxia due to cblC deficiency. Treatment with hydroxocobalamin, betaine, and folate resulted in biochemical and clinical improvement. This case highlights the importance of considering inborn errors of metabolism (IEMs) in patients of all ages presenting with altered mental status because appropriate diagnosis and treatment can improve outcome.

CASE REPORT

A 13-year-old sexually active girl presented to the pediatric emergency department with altered mental status. Her family reported that over the past month, the patient suffered from visual hallucinations, disturbed sleep, confusion, anorexia, and difficulty with activities of daily living. The family confirmed normal weight and cognitive development until about a month earlier when they noted poor oral intake, weight loss, and changes in the patient's mentation.

The adolescent's medical history included recent candidal vulvovaginitis, urinary tract infections, and musculoskeletal pain. She continued to complain of dysuria and abdominal, back, and neck pain. Upon further questioning, she revealed a history of sexual abuse and forced use of unknown illicit substances. Because her parents were divorced, she resided in multiple households and had no full siblings. Her family medical history was unremarkable.

Review of the patient's growth chart revealed a 5.5-kg weight loss. On physical examination, she was quiet and confused with poor eye contact and flat affect. Her neurologic examination, limited by her altered state, was notable only for marked psychomotor retardation. Her abdomen was diffusely tender to palpation, although her genitourinary examination was normal. Given her mental status, psychiatry was consulted, and she was admitted to the hospital for further management.

Preliminary laboratory evaluation showed neutropenia and microcytic anemia, which improved with nutrition and iron supplementation. A comprehensive metabolic panel, thyroid function tests, B_{12} level, folate level, and urine drug screen were unremarkable. An extensive infectious workup was also negative, including testing for syphilis, HIV, and other common viral etiologies. Because the patient was sexually active and had genitourinary complaints, she was treated presumptively for gonorrhea and *Chlamydia*.

On psychiatric evaluation, a preliminary diagnosis of acute stress disorder was made. Despite treatment with lorazepam and fluoxetine, the patient experienced no significant improvement in her mental status. Because the medical workup was inconclusive, the patient was transferred to the psychiatric hospital, where she was later observed to have seizure activity and ataxia. Although symptoms were initially attributed to pseudoseizures, additional neurologic studies were undertaken. Computed tomography of her head was normal, but magnetic resonance imaging revealed increased T2 signal in the cerebellum, and electroencephalography demonstrated a left temporal epileptic focus and diffuse encephalopathy. She was started on an antiepileptic (levetiracetam), which improved her electroencephalographic findings and mental status but not her clinical seizure activity. Further evaluation at that time included testing for less common etiologies.

Additional laboratory tests and assessment of the cerebrospinal fluid for infectious, paraneoplastic, and rheumatologic conditions was unrevealing. Thus, the diagnosis remained elusive. Pediatric genetics was consulted later in the workup because IEMs were thought to be unlikely given the patient's age. Metabolic testing, which included plasma amino acids (PAA), total plasma homocysteine, acylcarnitine, and urine organic acids (UOA) profiling, eventually led to the diagnosis.

PAA analysis showed the presence of homocystine with methionine at the lower limit of normal (Table 1). Total plasma homocysteine was also significantly elevated, indicating hyperhomocysteinemia (Table 1). The acylcarnitine profile showed elevated propionylcarnitine (C3) and C4 dicarboxylate species. UOA analysis showed elevated methylmalonic, methylcitric, and 3-hydroxypropionic acid (Table 1). Given the normal B_{12} level, hyperhomocysteinemia, elevated C3 in her plasma, and elevated methylmalonic acid in her urine, the patient was

TABLE 1 Metabolic Laboratory Values Before and After Treatment

Months into treatment	Plasma Amino Acids			Plasma Methylmalonic Acid	Plasma Acylcarnitine Profile			UOAs		
	Homocystine	Total homocysteine	Methionine		Propionyl-carnitine (C3)	C4-dicarboxylic	Methylmalonic	Methylcitric	3-Hydroxy-propionic
	RV: <1 (μmol/L)	RV: 5–15 (μmol/L)	RV: 7–47 (μmol/L)	RV: <0.4 (μmol/L)	RV: <1 (μmol/L)	RV: <0.09 (μmol/L)	RV: <7 (mmol/mol Cr)	RV: <8 (mmol/mol Cr)	RV: <26 (mmol/mol Cr)
0	13	178	8	N/A	4.32	0.51	>2500	54	264
1	0	27.2	31	N/A	0.44	0.24	81	12	24
4	N/A	75.3	N/A	N/A	N/A	N/A	283	18	83
6	0	46.3	22	30.99	3.66	0.22	677	22	59

Cr, creatinine; N/A, not available; RV, reference value.

diagnosed with a disorder of intracellular cbl metabolism likely involving complementation group cblC, although groups cblD, cblF, or cblJ remained in the differential pending definitive testing. She was started on 250 mg/kg/day of oral betaine daily, 1 mg of intramuscular hydroxocobalamin daily, and 5 mg of oral folate daily, which resulted in improvement in her weight, mental status, and biochemical parameters (Table 1). Her BMI improved from a nadir of the eighth percentile during admission to approximately the 40th percentile after discharge.

Follow-up laboratory values several weeks into treatment demonstrated undetectable homocystine and higher methionine levels on PAA profile, lower plasma total homocysteine levels, normalized acylcarnitine profile, and improved methylmalonic, methylcitric, and normal 3-hydroxypropionic acid on UOA profile (Table 1). Six months into therapy, her laboratory values continued to fluctuate but were not as high as before treatment (Table 1). The major clinical management challenge remains intermittent adherence to the prescribed regimen likely due to unresolved familial and social stressors.

Because cblC deficiency due to mutations in the *MMACHC* gene is the most common cause of combined hyperhomocysteinemia and methylmalonic aciduria, molecular testing for *MMACHC* was obtained and revealed that the patient was a compound heterozygote for 2 mutations, c.271dupA and c.482G>A. When approached, her parents declined carrier testing.

DISCUSSION

This case is an example of an IEM presenting later in childhood, a time period during which IEMs are not routinely considered in initial workup. A high index of suspicion is required when evaluating older children for cbl IEMs, given their nonclassic, heterogeneous phenotypes. Typically, adolescents with cblC deficiency do not present with the more classic symptoms that can be seen in infants. The disorder is suspected in infants presenting with failure to thrive, developmental delay, seizures, and acidosis.[3,5,14] In contrast, the only unifying characteristic in older patients with cblC deficiency is varying degrees of neuropsychiatric symptoms.[5] Ataxia with cerebellar findings on magnetic resonance imaging, as was found in this patient, has only been reported in 1 previous case.[16] Seizures, which were key in prompting additional testing in our patient, are uncommon in young adults, previously reported in only 3 older patients.[15,16] Anorexia, which was a prominent feature in this patient, has not been previously reported in late-onset cblC deficiency.[5] Although we cannot be certain if her weight loss was due to disease or to concomitant psychosocial influences, her weight and appetite improved, likely as a consequence of treating her underlying condition.

As seen with this case, recognizing an IEM can be difficult. The development of newborn screening (NBS) has assisted in early detection of IEMs in neonates. NBS can detect elevated C3, which can be increased in cblC, cblD variant 2, and cblF deficiencies and thus can aid in early diagnosis of these disorders. Unfortunately, NBS was not helpful in our patient because the expanded program was not implemented in Tennessee until 2004, 5 years after this patient was born.[17] The current Tennessee NBS cutoff value for C3 is 6.35 μmol/L (measured from a filter paper). On presentation, our patient's C3 value was 4.32 μmol/L (Table 1). It is of course unknown whether our patient's C3 levels would have been high enough on day 2 after birth to cross the current threshold.

When an IEM, such as cblC, is suspected based on clinical signs or NBS results, diagnostic workup relies on detection of abnormal concentrations of plasma and/or urine metabolites (Table 1). More specific

analyses, such as biochemical and molecular testing, can determine the specific deficiency and associated mutations.[3,14,18] Sequencing the gene (*MMACHC* located at 1p34.1[12]) for the most common complementation group (cblC) confirmed our diagnosis.

Our patient had 2 heterozygous mutations: c.271dupA and c.482G>A. The former is a duplication resulting in a frameshift/nonsense mutation on exon 2, causing premature protein truncation (predicted protein p.Arg91LysFsX14).[13] This mutation is found in ~40% of patients with cblC deficiency.[12] Most present with early-onset disease, which occurs when c.271dupA is present in homozygosity or in trans with another early-onset allele.[12] However, compound heterozygosity of this mutation with a missense mutation, such as c.482G>A on exon 4 (predicted protein p.Arg161Gln), tends to result in late-onset disease, which may be due to higher expression of the late-onset allele compared with the early-onset allele.[12,13,19–22]

Two other case reports have described patients who were also compound heterozygotes for c.271dupA and c.482G>A (Table 2).[20,23] Both patients presented with neuropsychiatric, hematologic, genitourinary, and musculoskeletal complaints, similar to our patient. Our patient differed from these cases in that she did not have a thrombotic event. Weight loss was not reported in either case; in fact, 1 patient was obese. Three genetic studies have identified the same mutations in a few individuals: 4 with late-onset disease,[12,21] 1 with early-onset disease, and 1 symptom-free sibling.[13]

Our patient was treated effectively with intramuscular hydroxocobalamin and oral betaine—an established treatment regimen.[14] High concentrations of hydroxocobalamin might stabilize the mutated cblC protein.[24,25] Betaine increases remethylation of homocysteine to methionine.[1,14] The addition of folate may also help with remethylation, but no longitudinal studies have documented

TABLE 2 Reported Cases of Compound Heterozygotes for c.271dupA and c.482G>A

References	Age at diagnosis (y)	Prominent Signs/Symptoms						Total homo-cysteine (μmol/L)	Plasma methio-nine (μmol/L)	Urine MA (mmol/mmol Cr)	Serum MA (μmol/L))
		Neuropsychiatric	Weight	Hematologic	Genitourinary	Musculo-skeletal	Other				
Bodamer et al (2001)[23]	20	Forgetfulness, sleepiness, slowed speech, encephalopathy	N/A	Deep venous thrombosis	Incontinence	Lower extremity paraplegia and areflexia, upper extremity weakness and hyperreflexia	Respiratory depression	27.9	N/A	1722	N/A
Tsai et al (2007)[20]	36	Hearing loss, depression, psychosis, peripheral neuropathy	Obesity	Spinal infarct	Urogenital fistula, urinary tract infections, uterine prolapse and hemorrhage	Hypermobile joints, arthritis, myopathy	Cataracts	57	0.0312	N/A	21.696
Present case (2013)	13	Visual hallucinations, disturbed sleep, confusion, psychomotor retardation, psychosis, acute stress disorder, ataxia, seizures	Anorexia	Anemia, neutropenia	Dysuria, candidal vulvovaginitis, urinary tract infections	Back pain, neck pain	N/A	178	8	>2500	N/A

Cr, creatinine; MA, methylmalonic acid; N/A, not available;

this.[14] Protein restriction is occasionally used, although its benefits have not been clearly proven.[5,14] No treatment regimen reverses all symptoms, but earlier treatment seems to result in better clinical outcomes.[14]

CONCLUSIONS

We describe an adolescent patient with cblC deficiency who displayed a novel late-onset phenotype associated with anorexia, ataxia, and seizures. Previous cases with the same mutations also presented with neuropsychiatric, hematologic, genitourinary, and musculoskeletal symptoms, similar to our patient. However, our patient is only the fourth reported case of seizures and only the second case of ataxia in late-onset disease. Moreover, no previous case of late-onset disease resulting from any mutation has presented with weight loss, which resolved with treatment. In conclusion, in addition to adding to the phenotypic spectrum of cblC deficiency, our case demonstrates that it is important for general pediatric physicians to consider IEMs while evaluating older children, especially given that specific treatment can result in an improved prognosis.

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