

## Cobalamin C Deficiency: Case Report of Two Different Clinical Presentations

Mehmet Gunduz<sup>1</sup>, Ozlem Unal<sup>1</sup>, Birce Dilge Taskin<sup>2\*</sup> and Zeynep Selen Karalok<sup>2</sup>

<sup>1</sup>Department of Pediatric Nutrition and Metabolic Diseases, Ankara Children's Hematology Oncology Training and Research Hospital, Ankara, Turkey

<sup>2</sup>Department of Pediatric Neurology, Ankara Children's Hematology Oncology Training and Research Hospital, Ankara, Turkey

### \*Correspondence to:

Birce Dilge Taskin, MD  
Department of Pediatric Neurology  
Ankara Children's Hematology Oncology  
Training and Research Hospital  
Diskapi/Ankara 06110, Turkey  
Tel: +90 532 490 42 22  
E-mail: [birdilge@gmail.com](mailto:birdilge@gmail.com)

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### Abstract

Cobalamin C deficiency (CblC) is the most frequent inborn error of cobalamin (Cbl) metabolism, which has a wide clinical spectrum. Cbl C defect causes the accumulation of methylmalonic acid and homocysteine and decreased methionine synthesis. Here we presented two distinct clinical forms of patients with CblC. First patient with early onset form was presented with failure to thrive, mild hypotonia, megaloblastic anemia and leukopenia at 2.5 months old. Second patient was presented with mental status changes, loss of speech, inability to walk and megaloblastic anemia at 12 years old. Laboratory analysis showed hyperhomocysteinemia, low plasma methionine levels and high urinary methylmalonic acid in both patients. Molecular analysis supported the diagnosis of CblC and treatment resulted in improvement of biochemical abnormalities, and neurologic findings in both patients.

### Keywords

Cobalamin C deficiency, Early-onset form, Late-onset form, Magnetic resonance imaging, Methylmalonic aciduria

### Introduction

The clinical manifestations of intracellular cobalamin (cbl) metabolism disorders can be highly variable [1]. Cobalamin C deficiency (CblC) is the most frequent inborn error of Cbl metabolism. The *MMACHC* gene, which is responsible for CblC, is on chromosome 1p23.2 [2]. Cbl C defect causes the accumulation of methylmalonic acid (MMA) and homocysteine and decreased methionine synthesis [3]. CblC is categorized into two clinical forms based on the onset age of the disease, including early and late onset [2, 4]. Patients presenting symptoms before one year of age are defined as early onset, whereas those presenting clinical signs later are defined as late onset [3]. These two forms have significant variability in clinical presentation, survival and prognosis. Early-onset group of CblC patients show feeding difficulties, failure to thrive, hypotonia, developmental delay/mental retardation, microcephaly, nystagmus, visual impairment, seizures and lethargy, followed by progressive neurological deterioration and coma. In contrast, major clinical findings of late-onset CblC group are cognitive and psychiatric problems such as confusion, disorientation; myelopathy, gait abnormalities and incontinence [2-4]. Here we presented two distinct clinical forms of patients with CblC deficiency.

## Case One

A 2.5-months-old boy was hospitalized failure to thrive, mild hypotonia, megaloblastic anemia and leukopenia to evaluate the etiology of. He was born at term, under an uneventful delivery. His parents were non-consanguineous. He was the second child, and first sibling was healthy. There is no family history of metabolic diseases.

The patient was malnourished weighing 4000 g (<3<sup>rd</sup> percentile), mildly hypotonic and pale at his first admission. Laboratory investigations revealed; Hb: 7.6 g/dL, N: 10.5–14 g/dL; MCV: 100.1 fL, N: 81.4–91.9 fL; WBC: 3500/mm<sup>3</sup> N: 5000–15000/mm<sup>3</sup>; absolute granulocyte count: 500/mm<sup>3</sup> (N: 1000–8500/mm<sup>3</sup>), liver enzymes, renal functions and electrolytes were within normal limits. Vitamin B12: 1033 pg/mL (N: 145–914 pg/mL). Reticulocyte was 4.97% (0.6–2.6%), and elevated. Cranial Magnetic Resonance Imaging (MRI) showed hyperintensity on T1 weighted images confluence of sinuses and left lateral sinus. Magnetic resonance venography demonstrated thrombosis of left lateral sinus. Coagulation parameters were normal. Homocysteine level was found highly elevated (78 µmol/L N: 3.3–8.3). Methionine level was at lower normal limits (14 µmol/L N: 10–53). Urine organic acid analysis showed 22 folds elevated MMA.

Developmental delay, megaloblastic anemia, hyperhomocysteinemia, cerebral venous sinus thrombosis, and elevated urine methylmalonic acid excretion were suggested cobalamin metabolism defect. Molecular analysis revealed compound heterozygote NM\_015506.2 (*MMACHC*): c.142A>G (p.I48V) / c.394C>T (p.R132\*) mutation (MIM 611935) and CblC defect was confirmed.

Hydroxocobalamin injections were commenced daily for 7 days followed by three times weekly injections (1 mg/day, i.m.). Oral folic acid (5 mg/day) and oral betaine (100 mg/kg/day) were started for hyperhomocysteinemia, and cerebral venous sinus thrombosis was treated with enoxaparin sodium. He is now two years old, he can walk with support, and has a few words. His last serum homocystein level was 16 µmol/L, and methionine was 26 µmol/L. Urine organic acid analysis showed 0.5X elevated methylmalonic acid. Ophthalmologic evaluation was normal other than refractive error. He had bilateral -2.5 D of myopia.

## Case Two

Previously healthy 12-year-old boy presented to the emergency department with a 1-week history of mental status changes, loss of speech and inability to walk. He was the first child of consanguineous Turkish parents. There is no family history of metabolic diseases. His perinatal period was normal, however developmental milestones were mildly delayed. He achieved head control at 3.5 months, succeeded in sitting without support at 12 months, and could walk without help at 18 months. He completed primary school and is going to secondary school, but there was a history of learning disability.

On neurologic examination; he was uncooperative, a marked flaccid paraparesis with urinary and fecal incontinence

was found. Lower limb deep tendon reflexes were absent, in contrast to the presence of a bilateral Babinski sign. He has unremarkable optic nerve and retinal examination.

In laboratory investigation; venous blood gas, blood lactate, electrolytes, liver and kidney function tests were normal. Serum studies for infectious (erythrocyte sedimentation rate, C-reactive protein), autoimmune (thyroid function tests, antinuclear antibody) were found to be within normal limits. Complete blood count showed macrocytic anemia (Hb: 8.7 g/dL, N: 10.5–14 g/dL; MCV: 99.6 fL, N: 81.4–91.9 fL). Vitamin B12 level (1020 pg/mL; reference range >200 pg/mL) was normal. Total folate (>23.2 ng/mL, N: 3.1–19.9 ng/mL) was increased, possibly secondary to a methylfolate trap from a dysfunctional cobalamin pathway. Electromyography (EMG) revealed a mild lower limb predominant demyelinating polyneuropathy.

During hospitalization, he developed focal seizures needing treatment with levetiracetam. Electroencephalogram (EEG) showed diffuse low-amplitude slow waves. He was treated with intravenous immune globulin (400 mg/kg per day intravenously for 5 days; total dosage 2 g/kg) followed by pulse methylprednisolone (1 g/day intravenously for 5 days) for presumed autoimmune encephalopathy. Then he was started on oral prednisolone therapy (1 mg/kg/day), however, his clinical status continued to fluctuate. Three weeks after admission, he developed right femoral vein thrombosis, which was treated with anticoagulant therapy. Screening for A1298C MTHFR mutation was heterozygous positive.

Metabolic investigation revealed high plasma homocysteine (80 µmol/L; N: 0–13 µmol/L), high urinary MMA (225 µmol/mmol creatinine; normally not detectable) and low plasma methionine levels (7.9 µmol/L; N: 10–53 µmol/L). These findings suggested the cobalamin defects. Molecular diagnosis by gene *MMACHC* (MIM 611935) sequencing analysis was performed, and revealed homozygous NM\_015506.2 (*MMACHC*): c.394C>T (p.R132\*) mutation.

Hydroxocobalamin injections were commenced daily for 7 days followed by three times weekly injections (1 mg/day, i.m.). In addition, oral folic acid (5 mg/day) and betaine (150 mg/kg/day) were started. Four months later after treatment, he progressively recovered his ability to walk with support. Plasma homocysteine and urine MMA levels decreased and, clinically his speech and walking improved.

His initial cranial MRI (before treatment) showed cortical atrophy and bilateral focal hyperintensities in the white matter at the level of centrum semiovale. T2 and Fluid-attenuated inversion recovery (FLAIR) hyperintensities were observed of posterior parietal periventricular white matter (Figure 1A). Second MRI, performed 3 months later after treatment, revealed slightly reduction of hyperintensities in the white matter (Figure 1B).

## Discussion

Herein, we presented one patient with late-onset and one patient with early-onset CblC. The diagnosis of intracellular

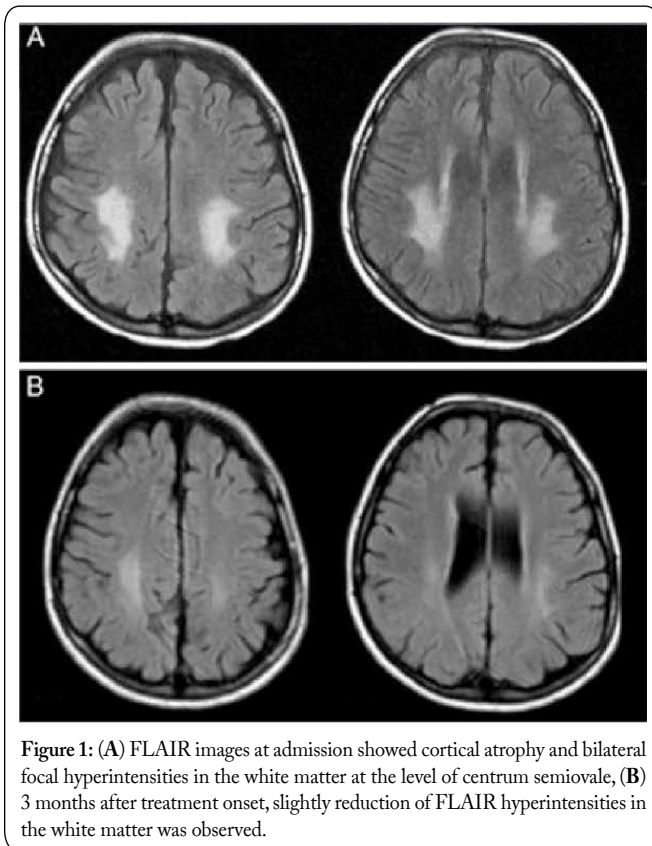


Figure 1: (A) FLAIR images at admission showed cortical atrophy and bilateral focal hyperintensities in the white matter at the level of centrum semiovale, (B) 3 months after treatment onset, slightly reduction of FLAIR hyperintensities in the white matter was observed.

cobalamin metabolism disorders relies on clinical, biochemical, and molecular genetic data. Urine organic acid and plasma amino acid analysis are the mainstays of biochemical testing. Diagnosis is confirmed by identification of biallelic mutation in *MMACHC* gene [1]. In our patients, hyperhomocysteinemia, low methionine levels and neurologic findings suggested CblC, and diagnosis was confirmed with molecular genetic analysis. Failure to thrive, cytopenias, global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures are typical for early-onset [1]

Developmental delay, hypotonia, megaloblastic anemia, leukopenia, hyperhomocysteinemia were detected in our early-onset patient. Diversely, individuals with adolescent and adult presentation usually have predominant neurologic and neuropsychiatric manifestations [1]. Our late-onset patient had only mildly developmental delay and learning disability until 12-year-old. He was presented with severe flaccid paraparesis and loss of conscious. He benefited from treatment but had neurologic sequelae. Although the metabolic derangement may be considered as equal in two distinct phenotypes, clinical findings differ even in the different patients manifesting same phenotype.

Clinical and laboratory findings improved with hydroxocobalamin, oral folic acid, and betaine treatments. Protein restriction was not commenced. Patients with CblC treated with medical foods designed for isolated methylmalonic acidemia are at risk for iatrogenic methionine deficiency that could adversely affect brain growth and development [5].

In our patients, MTHFR mutation was screened in Case II. Cause elevated MMA and homosistein levels along with

low to normal serum methionine levels are sensitive indicators for deficiency of methylcobalamin and adenosylcobalamin synthesis including CblC. MTHFR deficiency is the most common inherited disorder of folate metabolism. The most severe phenotype represents the neonatal form. Stroke, thromboembolic complications, progressive spastic paraparesis, seizures may be seen in adult onset cases. Homocysteinemia and low to normal serum methionine levels are also characteristics for MTHFR deficiency, although lack of methyl malonic aciduria is an important finding that could differentiate these two disorders [2, 6].

Previously, brain MRI abnormalities in CblC have been reported several times in the literature. Longo et al. observed unusual basal ganglia lesions in 30% of seven patients who have early-onset type CblC. Additionally, a high incidence of hydrocephalus and supratentorial white matter abnormalities (43%) were found [7]. Findings in our patients are different and also much less severe than shown in this study. Brain MRI findings of late-onset type patients are rare and limited to case reports. In the clinical report of Gurkas et al., brain MRI of the late-onset type CblC patient before treatment showed bilateral patchy focal hyperintensities in the white matter and cortical atrophy. After treatment, normalization of MRI findings was achieved as similar as our late-onset type CblC patient [8].

Lerner-Ellis et al. sequenced *MMACHC* gene from the gDNA of 118 CblC individuals. Genotype-phenotype correlations of common mutations were apparent; individuals with c.394C>T tend to present with late-onset disease whereas patients with c.331C>T and c.271dupA tend to present in infancy [9]. Our late-onset patient was homozygous for c.394C>T that is one of the most seen mutation in European population, and showing a tendency for late-onset presentation. Our early-onset patient was also heterozygous for c.394C>T and, the other allele was showed p.I48V (c.142A>G). The latter may be associated with early-onset presentation. In a previous publication, Matos et al. reported 5 separated early onset CblC patients. All of them had two heterozygote mutations which may lead to earlier presentation as similar as our early onset type CblC patient [10].

Kilic et al. presented a Turkish patient who had neurological impairment at the age of four years as presented with late-onset CblC. Homozygous c.394C>T; p.R132\* mutation in the *MMACHC* gene was detected. Cranial MRI showed bilateral signal intensity changes in the basal ganglia and cerebral white matter and diffuse atrophy of the corpus callosum and cerebrum [10]. In our patient, initial MRI showed cortical atrophy and bilateral focal hyperintensities in the white matter. c.394C>T mutation is common in the Asiatic-Indian/Pakistani/Middle Eastern populations. There is no report on the frequency and distribution of *MMACHC* gene mutations in the Turkish population [11].

Patients with early-onset CblC and *MMACHC* mutations showed an early-onset, unusually fast-progressing maculopathy with severe central outer nuclear layer and ganglion cell layer loss [12]. Brooks et al. reported ophthalmic manifestations, and long term visual outcomes in 25 patients

**Table 1:** The major diagnostic findings of the presented patients and short summary of the literature.

Case	Age of Presentation	Clinical Findings	Laboratory Findings	Brain MRI	Molecular Analysis (MMACHC genotype)
Ben-Omran, 2007 [4]	14 years	Depression, regression, school failure, dementia, lactic acidosis, peripheral neuropathy, incontinence, ataxia, lethargy, seizures	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Diffuse cerebral atrophy	Homozygous R132X mutation
Ben-Omran, 2007 [4]	10 years	Learning disorder, school failure, acute dementia, anorexia, weight loss	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Normal	Homozygous R132X mutation
Heil, 2007 [14]	13 years	Cognitive regression, macrocytic anemia, marfanoid features	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Data not available	Heterozygous c.271 dup A p.Arg91LysfsX14 and c.1A>G p.Met1 mutations
Heil, 2007 [14]	10 years	Developmental delay, behavioral abnormalities	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Data not available	Heterozygous c.271 dup A p.Arg91LysfsX14 and c.1A>G p.Met1 mutations
Matos, 2013 [10]	1 month	Feeding difficulties, failure to thrive, hypotonia, pyramidal signs, seizures, megaloblastic anemia	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	White matter alterations	Heterozygous c.271 dup A/c.271 dup A p.Arg91LysfsX14/p.Arg91LysfsX14 mutations
Matos, 2013 [10]	21 days	Feeding difficulties, failure to thrive, vomiting, hypotonia	Data not available	White matter alterations	Heterozygous c.271 dup A/c.615 c>G p.Arg91LysfsX14/p.Tyr205X mutations
Matos, 2013 [10]	16 days	Feeding difficulties, failure to thrive, irritability, hypotonia, blood cytopenias, megaloblastosis	High plasma homocysteine and methylmalonic acid	Not done	Heterozygous c.271 dup A/c.271 dup A p.Arg91LysfsX14/p.Arg91LysfsX14 mutations
Matos, 2013 [10]	16 days	Feeding difficulties, failure to thrive, hypotonia, blood cytopenias, nystagmus	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Not done	Heterozygous c.271 dup A/c.271 dup A p.Arg91LysfsX14/p.Arg91LysfsX14 mutations
Matos, 2013 [10]	2 months	Feeding difficulties, failure to thrive, vomiting/GE reflux, global developmental delay, microcephaly, hypotonia, myoclonic seizures, dysmorphic features (flat filtrum, triangular upper lip), nystagmus, anemia	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	White matter alterations	Heterozygous c.271 dup A/c.271 dup A p.Arg91LysfsX14/p.Arg91LysfsX14 mutations
Gurkas, 2015 [8]	8 years	Behavioral abnormalities, sleep problems, school failure, seizures	High plasma homocysteine, low plasma methionine, elevated urine methylmalonic acid	Cortical atrophy, patchy focal hyperintensities in the white matter	Homozygous c.394C>T (p.R132X) mutation
Krueger, 2015 [15]	8 years	Encephalopathy, speech difficulties, acute regression, seizures	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Mild-moderate volume loss	Homozygous c.394 C>T mutation
Current Case 1	2.5 months	Failure to thrive, mild hypotonia, megaloblastic anemia, leukopenia, developmental delay	High plasma homocysteine and methylmalonic acid, elevated urine methylmalonic acid	Hyperintensity on confluence of sinuses and left lateral sinus	Compound heterozygote c.142A>G (p.I48V) / c.394C>T (p.R132*) mutation
Current Case 2	12 years	Mental status changes, loss of speech, inability to walk, urinary and fecal incontinence, seizures	High plasma homocysteine, low plasma methionine, elevated urine methylmalonic acid	Cortical atrophy and bilateral focal hyperintensities	Homozygous c.394C>T (p.R132*) mutation

with CblC deficiency [13]. Nystagmus, strabismus, macular degeneration, optic nerve pallor, and vascular changes were

frequent ophthalmologic findings in their study. In our patient with early-onset, ophthalmologic examination showed

refractive error. It is important to follow up of ophthalmologic findings in this patient. In contrast, eye findings were totally normal in our other patient with late-onset.

In conclusion, both early and late-presented CblC could lead to severe neurologic and ocular findings. Variability in disease expression is elucidated by Table 1 including the major diagnostic findings of the presented patients and short summary of the literature. Both early and late onset CblC may improve with hydroxocobalamin, folic acid, and oral betaine treatments. Cranial imaging and genotype may be correlated in part with the age of presentation.

### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

### Author Contributions

MG, OU and BDT wrote the manuscript. MG, OU and BDT were involved in the diagnosis. MG, OU, BDT and ZSK were involved in the management of the patient. OU and BDT edited the manuscript. All authors read and approved the final manuscript.

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