Diverse Clinical manifestations of Cobalamin C Metabolism Disorders

Hosein Eslamiyeh, MD [1]

[1] Children Growth Disorder Research Center, Department of Pediatrics, Shahid Sadoughi University of Medical Science, Yazd, Iran

Keywords:

Cobalamin C deficiency
Methylmalonic acidemia and homocystinuria
Cerebellar Ataxias
Epilepsies
Hydroxycobalamin

Received:
13-Apr-2024
Accepted:
30-Sep-2024
Published:
11-Mar-2025

ABSTRACT

Cobalamin, commonly known as vitamin B12, is a crucial micronutrient synthesized predominantly by a few microorganisms. In the human body, Vitamin B12 (Cobalamin) is essential for DNA synthesis and is required as a cofactor for functioning two crucial enzymes, methylmalonyl-CoA mutase and methionine synthase. The deficiency in these cobalamin-derivated coenzymes leads to enzyme activity dysfunction and an accumulation of their respective substrates, methylmalonic acid, and homocysteine,harming the brain and many other organs. Furthermore, deficiency in this micronutrient can lead to a wide spectrum of hematologic and neuropsychiatric disorders. In addition to vitamin B12 deficiency, some genetic disorders block the intracellular processing of Cobalamin to its cofactors and lead to symptoms somewhat similar to vitamin B12 deficiency. These disorders are called Cobalamin metabolism disorders. Many of them are reversible when diagnosed early and treated promptly. This group's most common and well-understood disease is Cobalamin C (CblC) metabolism disorder. This case series report aimed to provide a comprehensive overview of diverse clinical presentations within the spectrum of CblC metabolism disorder and the introduction of two cases of late-onset presentation with ataxia and repeated seizures as the first manifestation of the disorder. Few case reports are available, specifically in children, describing cerebellar ataxia and seizure as the first manifestations of late-onset CblC metabolism disorder. Additionally, this report sought to contribute to the existing literature by highlighting potential areas for timely recognition and targeted clinical and therapeutic interventions, thereby enhancing the comprehensive care and support for individuals affected by CblC metabolism disorder.

How to cite this article: Eslamiyeh H. Diverse Clinical manifestations of Cobalamin C Metabolism Disorders. Iran J Child Neurol. 2025; 19(2): 131-141. https://doi.org/10.22037/ijcn.v19i2.45047

*__Corresponding Author:__ Eslamiyeh H, MD. Shahid Sadoughi University of Medical Science, Yazd, Iran. Email: eslamieh@ssu.ac.ir

Introduction

Cobalamin, commonly known as vitamin B12, is a crucial micronutrient synthesized predominantly by a few microorganisms (1). Due to this limited synthesis, animals, including humans, rely on dietary sources for their intake. Among the water-soluble vitamins, vitamin B12 stands out as one of the most chemically complex. The pivotal role of Cobalamin was initially discovered by Smith and Rickes (2.3) following the groundbreaking work of Minot and Murphy, who demonstrated the efficacy of oral liver extract in treating pernicious anemia (4). Vitamin B12 (Cobalamin) is essential for DNA synthesis and neurological function. Deficiency in this micronutrient can lead to a wide spectrum of hematologic and neuropsychiatric disorders, many of which are reversible when diagnosed early and treated promptly. In the human body, Cobalamin is required to function in two crucial enzymes—mitochondrial enzyme methylmalonyl-CoA mutase and cytoplasmic enzyme methionine synthase (5). The former mediates the conversion of methylmalonyl-CoA to succinyl-CoA and relies on adenosylcobalamin (AdoCbl) as a cofactor. Methylmalonyl-CoA arises during the breakdown of branched-chain amino acids and odd-chain fatty acids. The latter enzyme, methionine synthase, remethylates homocysteine to form methionine and necessitates another Cobalamin derivative, methylcobalamin, as a coenzyme. A deficiency in these Cobalamin-derivated coenzymes leads to enzyme activity dysfunction and an accumulation of their respective substrates—methylmalonic acid and homocysteine (6). Vitamin B12 is produced by only a few microorganisms, so animals must obtain it through their diet. In humans, the process of absorbing and transporting Cobalamin throughout the body is quite complex. In addition to vitamin B12 deficiency, some disorders block the intracellular processing of Cobalamin to its cofactors. These disorders, known as Cobalamin metabolism disorders, have a genetic basis and result in clinical symptoms similar to those of a B12 deficiency (7) (Figure 1).

The hallmarks of genetic disorders affecting Cobalamin metabolism are methylmalonic aciduria, homocystinuria, combined methylmalonic aciduria, and homocystinuria without dietary Cobalamin deficiency (8). Eight defects of intracellular Cobalamin metabolism have been identified by somatic complementation analysis. The prototypical and most well-understood phenotype is CblC; this disorder results in both homocystinuria and methylmalonic aciduria (9-12). The gene responsible for the *CblC* group, called *MMACHC*, was identified by homozygosity mapping in 2006(9). Traditionally, Cobalamin C(CblC) metabolism disorder is classified as early and late onset (10). Early-onset patients, presenting symptoms within the first year of life, show a multisystem disorder with severe neurological, hematological, and ocular manifestations. Late-onset disorder is characterized by milder clinical phenotype and psychiatric symptoms with slowly progressive neurological disorders. This classification is somewhat vague, and the disease symptoms among the patients of the same group are very diverse according to the patient's age, so another classification has been defined according to the age of initial presentation. In this classification, the onset time of symptoms is considered the basis of classification. This classification includes

- In utero presentation with fetal non-immune hydrops, heart failure, and intrauterine growth restriction.
- Newborns are characterized by microcephaly,

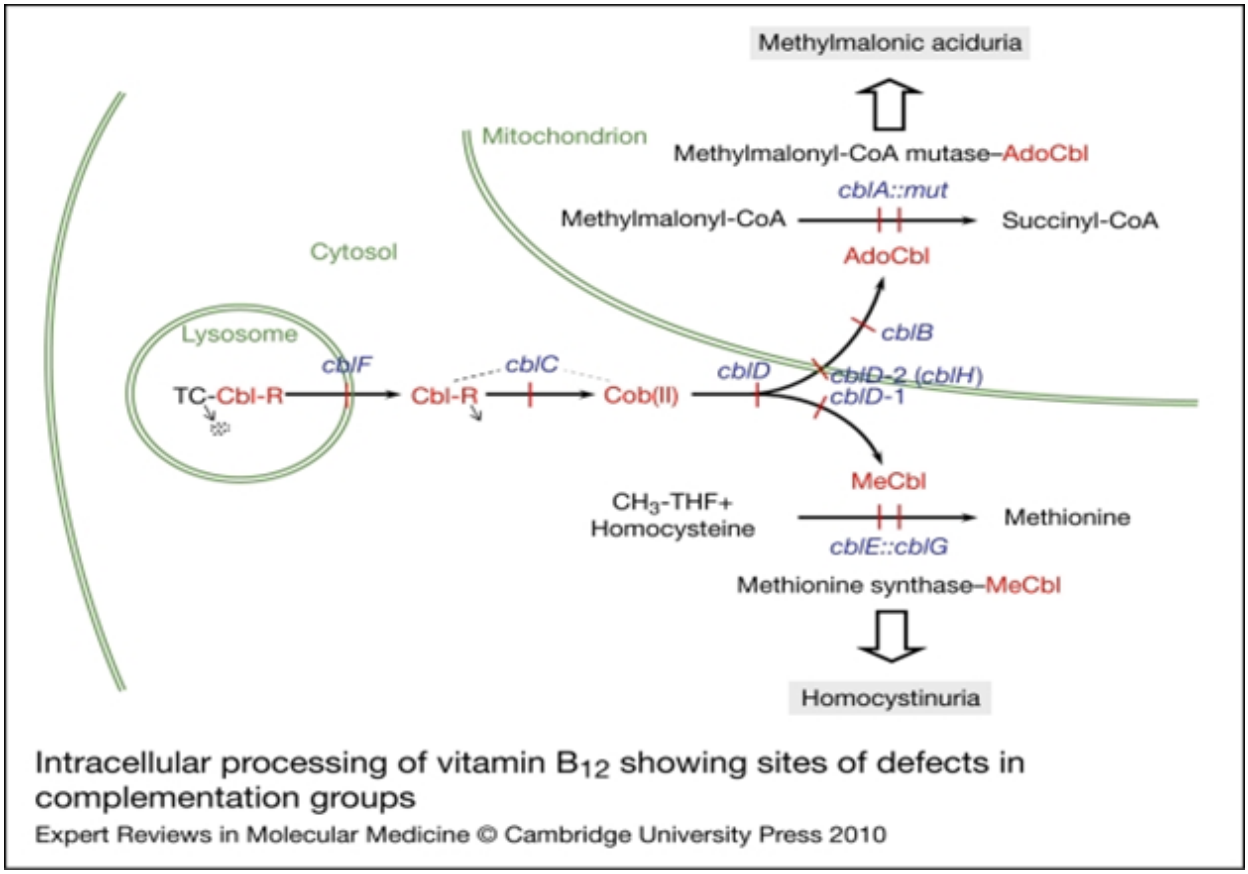

Figure 1. The image illustrates intracellular Cobalamine metabolism pathway and different complementaion groups

developmental delay, and encephalopathy.

• Infants exhibiting poor feeding, slow growth, developmental disorder, and occasionally hemolytic uremic syndrome (HUS).

• Toddlers with poor growth, progressive microcephaly, cytopenias (megaloblastic anemia), global developmental delay, encephalopathy, and neurological signs such as hypotonia and seizures. Adolescents and adults displaying neuropsychiatric symptoms, progressive cognitive decline, thromboembolic complications, and/or subacute combined degeneration of the spinal cord.Given the multifaceted nature of CblC metabolism disorders and the need for detailed clinical characterization, the objective of this case series report was to provide a comprehensive overview of diverse clinical presentations within the spectrum of CblC metabolism disorders and introduction of two cases of late-onset presentation with ataxia and repeated seizures as the first manifestation of disorder (11). By offering in-depth descriptions of varied manifestations observed across different age groups and contexts, this report aimed to enhance the understanding of the clinical intricacies associated with this condition and provide additional insights into the disease's diverse phenotypic expressions, particularly cerebellar ataxia as presenting sign of the disorder in late-onset disease (12). Additionally, this report sought to contribute to the existing literature by highlighting potential areas for targeted clinical management and therapeutic interventions, thereby enhancing the comprehensive care and support for individuals affected by CblC metabolism disorders (13). Through the detailed presentation of these

diverse clinical cases, we aimed to shed further light on the multifaceted nature of this disorder, elucidating potential areas for improved clinical care and management tailored to the specific needs of individual patients. This study introduces five significant cases with the final diagnosis of CblC metabolism disorder referred to the Pediatric Neurology Clinic and Emergency Ward of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, with diverse neurological symptoms during the last ten years. Two last cases (cases 4 and 5) have revealed fewer reported manifestations of late-onset CblC metabolism disorder (Ataxia and refractory epilepsy) in the pediatric population.

Case Presentations

Case 1

A 5-month-old female infant was presented at the Pediatric Neurology Clinic due to a lack of head control and absence of cooing. The child, born to consanguineous parents (cousins), was delivered by normal vaginal delivery with a birth weight of 2100 grams and a head circumference of 32 cm, indicating small for gestational age (SGA).

Normal heart and lung auscultation were reported upon physical examination, and no organomegaly was detected during abdominal examination. However, the observed head circumference of 32 centimeters was lower than the usual range for this age group, and brisk deep tendon reflexes were noted. Given the patient's history of being born small for gestational age and the observed developmental delay, brain Magnetic resonance imaging (MRI) and metabolic screening tests were conducted, including amino acid chromatography, ammonia, and lactate. The MRI revealed ventriculomegaly with periventricular hyperintensities, while metabolic screening tests disclosed elevated levels of homocysteine in the blood (homocysteine=284). To establish the etiology of the increased serum homocysteine, an acylcarnitine profile, and urine organic acids were measured, revealing a significant elevation of methylmalonic acid in both the urine and serum, along with an elevated level of homocysteine. As a result, a diagnosis of methylmalonic acidemia with homocystinuria was confirmed. Genetic studies identified a mutation in the MMACHC gene, confirming the CblC metabolism disorder diagnosis. Treatment with hydroxocobalamin and betaine was then initiated. Following three months of treatment, a marked improvement was observed in the patient's head control, and the serum level of homocysteine decreased to 58 mmol/liter. Considering the low birth weight at the time of birth and the presence of microcephaly, the disease trajectory indicates that this patient falls into the group with initial manifestations in the neonatal period or early onset disease.

Case 2

A 4-year-old boy was referred to the pediatric neurology clinic at our hospital due to a global developmental delay. He had been diagnosed with cerebral palsy at the age of four months and had undergone occupational and speech therapy for the past three years to aid in his development. Despite these interventions, the patient was unable to walk or sit independently, and his speech was limited to three to four words. He was the second offspring of consanguineous parents with no history of prenatal or perinatal insults. His birth weight was 3400 grams, and his birth head circumference was 34 cm. Previous investigations revealed mild ventriculomegaly with irregular ventricular borders in the brain MRI and a complete blood count showing low hemoglobin (Hb=10 g/dl) with elevated mean corpuscular volume

(MCV=94), indicative of macrocytic anemia. Following the indications of megaloblastic anemia from previous examinations, a repeated complete blood count and serum ferritin, vitamin B12, and folate levels were assessed. Metabolic tests were also conducted, including amino acid chromatography, acylcarnitine profile, urine organic acids, and homocysteine. The results indicated normal levels of vitamin B12 and folate, alongside increased methylmalonic acid and homocysteine, suggesting a possible cobalamin metabolism disorder, particularly CblC. Subsequently, genetic analysis confirmed the diagnosis of CblC metabolism disorder. Considering the patient's normal weight and head circumference at birth, alongside the disease course, it appears that this patient falls into the group with initial manifestations during infancy or early onset disease according to traditional classification.

Case 3

A 3-year-old boy was referred to our medical office due to regression, which began at 5 months of age. Prior to the onset of the illness, the child's development had been normal; at the age of four months, he exhibited appropriate head control and responses to stimuli. However, he gradually lost these abilities over 13 months. By the age of two, the patient began experiencing frequent seizures characterized by tonic stiffening of limbs and upward gaze. Despite efforts with various anti-epileptic medications, the seizures did not respond effectively, prompting the use of a combination of medications without substantial benefit. The child was the third offspring of consanguineous parents with normal prenatal and perinatal history, displaying normal weight and head circumference at birth. Earlier medical investigations, including brain MRI and amino acid chromatography, ammonia, and lactate, did not yield a definitive diagnosis for his illness. However, we incidentally discovered a complete blood count in his records, revealing a slightly decreased hemoglobin concentration (Hb=10.5 g/dl) with a mean corpuscular volume (MCV) of 85 fl and a normal mean corpuscular hemoglobin (MCH) and platelet count. Upon repeating the CBC, the hemoglobin level was 10.3 g/dl, with an MCV of 87 fl. This prompted consideration of macrocytic anemia, leading to the request for vitamin B12 level, folic acid, and acylcarnitine profile with urine organic acids. While vitamin B12 and folate levels fell within the normal range, examinations revealed methylmalonic acidemia with homocystinuria. Following this investigation, genetic studies ultimately confirmed the diagnosis of CblC metabolism disorder. With the patient's normal development until five months of age followed by subsequent regression, it is apparent that this patient falls into the group with initial manifestations during infancy or early onset disease.

Cases 4 and 5

An 11-year-old girl was brought to the pediatric emergency center with complaints of frequent seizures over the past two days, accompanied by regression in past medical history of herself and her sister.

The patient had a history of two focal seizures five months prior, managed with levetiracetam. Upon arrival at the emergency department, she experienced another seizure characterized by focal tonic stiffening of the left hand and jerky contraction of the right facial muscles, accompanied by upward eye deviation. The event evolved into a generalized status epilepticus

with tonic-clonic seizures lasting for over 40 minutes, ultimately controlled by loading doses of levetiracetam and phenytoin.

Following the cessation of the seizures, a comprehensive neurological and physical examination was conducted. The patient was the first offspring of non-consanguineous parents, born prematurely (at 34 weeks) due to a twin pregnancy, with no reported prenatal or perinatal complications. Her developmental history prior to the onset of the disease was unremarkable, and her weight (30 kilograms) and head circumference (50 centimeters) were in the normal range.

Neurological examination revealed an alert and cooperative patient with normal cranial nerves and deep tendon reflexes. However, a bilateral Babinski sign was detected, and cerebellar assessments were interrupted, including finger-to-nose and tandem gait. The patient's mother expressed concerns about her child's clumsiness and disequilibrium over the past 1.5 years, as well as her noticeable hand tremors, particularly during object handling (intention tremor), slurred speech, and poor academic performance, indicative of learning disability. Overall, the neurological examination suggested cerebellar ataxia and cerebellar involvement over the prior 18 months. Normal heart and lung auscultation were noted during the physical examination. No organomegaly was detected during the abdominal examination. Subsequently, the seizures recurred multiple times, leading to the administration of phenobarbital and midazolam drip.

A comprehensive array of laboratory and metabolic studies were conducted to elucidate the underlying cause of these seizures. Routine laboratory tests revealed normal glucose, calcium, electrolytes, liver and kidney function, and blood gas profiles. However, the complete blood count showed hemoglobin at 10.5 g/dl, mean corpuscular volume (MCV) at 95 fl, white blood cell count at 11000, and platelet count at 230000/mm3.blood gas profile reveaeled mild metabolic acidosis with PH=7.34 , PCO2=35 mmHg, HCO3=15 miliequivalent/liter . Given the discrepancy between the low hemoglobin level and the high MCV, the CBC was repeated, showing an MCV of 97fL. As a result of the elevated MCV and low hemoglobin, a diagnosis of megaloblastic anemia was proposed. Subsequently, vitamin B12 and folate levels were measured and found to be within the normal range (Vitamin B12 = 280 pg/ml [180-800], Folate = 8 ng/ml [2.5-20], respectively).

Additional metabolic studies were conducted, including acylcarnitine profile, urine organic acid analysis, homocysteine levels, and amino acid chromatography. Remarkably, a rapid response in homocysteine testing revealed a 43 Micromol/liter level. Given the neurological findings, featuring megaloblastic anemia with normal B12 and folate levels alongside high homocysteine levels and mild metabolic acidosis, the possibility of a cobalamin metabolism disorder became a focus of the investigation, prompting the initiation of intramuscular hydroxocobalamin injection. Following 20 days of treatment, a significant improvement was observed in the patient's ataxia and speech, with no recurrence of seizures.

Subsequent metabolic study results revealed methylmalonic aciduria with homocystinuria. Whole exome sequencing confirmed a mutation in the MMACHC gene, thereby establishing the diagnosis of CblC metabolism disorder. Interestingly, the patient's twin sister, who had a history of controlled focal seizures and the almost simultaneous onset of the disease with similar symptoms of cerebellar ataxia and regression,

was evaluated by genetic study, and the disease was confirmed for her. She was also treated by intramuscular injection of hydroxyl cobalamin and oral betaine. After a month of treatment, her symptoms improved significantly. According to late manifestations of the disease in the studied patients during adolescence, these patients fall into the group with initial manifestation in adolescence and adult period or late-onset disorder.

Discussion

The current case series report presented five cases revealing a range of CblC metabolism disorder presentations, shedding light on the diverse clinical manifestations and the utility of specific investigations in reaching a conclusive diagnosis. In the first case, we had an infant with a lack of head control and an absence of cooing. MRI examination revealed ventriculomegaly with periventricular hyperintensities and elevated homocysteine levels in the blood. She was diagnosed with methylmalonic acidemia with homocystinuria due to a mutation in the MMACHC gene. Consequently, she was treated with hydroxocobalamin and betaine, which improved head control and decreased serum homocysteine levels. Similarly, research by Lerner-Ellis et al. (2006) provided key insights into the MMACHC mutation, underpinning the CblC defect (14). Their work chronicled nearly 100 variants recorded in the Human Gene Mutation Database (HGMD) to date, each influencing RNA stability or residual function of the protein (14). This diverse array of variants was linked to potential variations in the phenotype and severity of the disease, emphasizing the multifaceted nature of these metabolic disorders.

A 4-year-old boy with global developmental delay was the second case. MRI examination of the brain revealed mild ventriculomegaly and blood tests indicative of macrocytic anemia. CblC metabolism disorder was confirmed, revealing the probability of CblC metabolism disorder manifestations onset during infancy.

Similarly, findings regarding the third case suggested the manifestations of this disorder during infancy. The present findings in these three cases were similar to those of other studies, such as the early onset cases reported by Fischer et al. and Huemer et al.'s studies (16, 17) (Table 1). In the two last cases, the patients experienced cerebellar ataxia, focal seizure, and regression as presenting signs of the disease. A limited number of case reports are available, specifically in children, that describe cerebellar ataxia and seizure as the first manifestations of late-onset cobalamin metabolism disorder. Ben-Omran et al. (2) reported a 14-years-old girl with similar symptoms to ours, including dementia, regression, and learning disability, two years before referral. Their patient developed incontinence, ataxia, lethargy, and generalized tonic-clonic seizures over a 4-month period. Extensive investigations were carried out for her, and finally, metabolic studies, including plasma amino acid chromatography and urine organic acids, revealed the diagnosis of methylmalonic aciduria with homocystinuria. Then, the genetic study confirmed CblC metabolism disorder. The patient experienced significant improvement in her clinical dementia, ataxia, and biochemical parameters with the administration of hydroxyl cobalamin, carnitine, and betaine. However, slight gait abnormality persisted.

In the studied patients, following the initiation of intramuscular cobalamin injection and oral betaine, after 20 days, a significant improvement was achieved in the patient's ataxia and speech,

Table 1. compares the clinical symptoms of our cases with other similar articles.(Nl= normal)

	Case 1	Case 2	Case 3	Case 4	Case 5	Ben omran et al	Huemer et al	Fischer et al
Birth weight	low	NL	NL	NL	NL	NL	NL	Low (a few cases) NL (most cases)
Birth Head Circumference	low	NL	NL	NL	NL	NL	Low (in some patients) NL (MOST CASES)	Low (in some patients) NL (MOST CASES)
Failure to thrive	+	+	+	-	-	-	+ (in early onset patients)	+ (in early onset patients)
Megaloblastic Anemia	+	+	+	+	+	+	+	+
Seizure	+	+	+	+	+	+	+	+
Regression	+	+	+	+	+	+	+	+
Cerebellar ataxia	-	-	-	+	+	+	+	-
Ocular manifestastions	-	+	-	-	-	+	+	+
Kidney disease	-	--	-	-	-	-	+	+

with no recurrence of seizures. After three months, all disease symptoms were removed, and no residual abnormality was detected (Table 1).

The outcomes from case 1, along with cases 4 and 5, offered valuable insights into how treatments targeting CblC metabolism disorders could be therapeutically beneficial. Initiation of hydroxycobalamin and betaine in case 1 resulted in demonstrable improvements in the patient's head control and serum homocysteine levels. Similarly, the administration of intramuscular Cobalamin injections in cases 4 and 5 led to significant amelioration of ataxia and speech, with a promising absence of seizure recurrence. These responses indicate the potential benefit of targeted therapies in managing the neurological manifestations of CblC metabolism disorder.

The diagnostic journey in this series of cases underscored the diverse initial presentation of the disorder, ranging from developmental delays to neurological regression, psychiatric changes, cerebellar ataxia, and seizures. Additionally, it revealed the critical role of thorough investigations in uncovering CblC metabolism disorder. These

findings emphasize the need for a high index of suspicion and a comprehensive approach when encountering patients with unexplained neurological and hematological findings.

Although the disease is treatable, the second key finding was the importance of timely recognition. Timely recognition by using specific tests such as acylcarnitine profiles and urine organic acids facilitated the detection of methylmalonic acidemia with homocystinuria. These metabolic clues played a vital role in steering the diagnostic process toward identifying CblC metabolism disorder. This underscores the significance of the timely use of specialized laboratory testing in the realm of metabolic disorders, showcasing their potential to shed light on intricate biochemical aberrations that might otherwise go unnoticed.

In Iran, the process of requesting metabolic tests until the answers are prepared takes a long time (between one to 6 months), and the importance of timely recognition and treatment of disease means we had to start treatment with hydroxy cobalamine before preparing a definite laboratory diagnosis. The genetic confirmation of MMACHC gene mutations in multiple cases solidified the diagnosis of CblC metabolism disorder, reinforcing the clinical significance of genetic testing in delineating the underlying etiology of metabolic abnormalities. Similarly, one study analyzing the complementation groups and their impact on clinical presentation, possibly resembling different phenotypes and age of onset, was conducted by Sean Froese and Gravel in 2010 (8). Their findings detailed how different complementation groups demonstrated specific blocks or deficiencies within the cobalamin metabolism pathway, leading to distinct manifestations and disease trajectories. Overall, these findings contribute to our comprehensive understanding of Cobalamin metabolism disorders, highlighting the need for personalized and nuanced care approaches that account for the diverse genetic and clinical presentations observed across different complementation groups.

Moreover, this case series sheds light on the potential utility of novel treatment modalities and the imperative role of ongoing research and clinical trials aimed at further understanding the pathophysiology and refining management protocols for CblC metabolism disorder.

In Conclusion

This case series report not only unraveled the fascinating presentations of CblC metabolism disorder ranging from developmental delay to neurological regression, psychiatric changes, cerebellar ataxia, and seizures but also emphasized the pivotal role of targeted investigations, timely recognition, and tailored interventions in delineating and managing of these complex metabolic and neurological conditions. Additionally, this underscores the need for a high index of suspicion and a comprehensive approach when encountering patients with unexplained neurological findings such as new onset progressive ataxia or refractory epilepsy.

Acknowledgment

The author would like to thank Dr. Mirhosseini, a pediatric endocrinologist, for helping manage patients. The authors also thank the patients and their families for contributing to the treatment and follow-up.

Authors' Contribution

Definite diagnosis of the cases and critical revision of the manuscript for important intellectual content: Hosein Eslamiyeh

Conflict of Interest

The author declared no conflict of interest.

References

1. Sobczyńska-Malefora A, Delvin E, McCaddon A, Ahmadi KR, Harrington DJ. Vitamin B12 status in health and disease: a critical review. Diagnosis of deficiency and insufficiency – clinical and laboratory pitfalls. Critical Reviews in Clinical Laboratory Sciences. 2021;58(6):399-429.
2. Ben-Omran TI, Wong H, Blaser S, Feigenbaum A. Late-onset cobalamin-C disorder: a challenging diagnosis. American Journal of Medical Genetics Part A. 2007;143(9):979-84.
3. Rickes EL, Brink NG, Koniuszy FR, Wood TR, Folkers K. Crystalline vitamin B12. Science. 1948;107(2781):396-7.
4. Smith AD, Warren MJ, Refsum H. Vitamin B12. Advances in food and nutrition research. 2018 Jan 1;83:215-79.
5. Mascarenhas R, Gouda H, Ruetz M, Banerjee R. Human B(12)-dependent enzymes: Methionine synthase and Methylmalonyl-CoA mutase. Methods in enzymology. 2022;668:309-26.
6. Wolffenbuttel BHR, Wouters H, Heiner-Fokkema MR, van der Klauw MM. The Many Faces of Cobalamin (Vitamin B(12)) Deficiency. Mayo Clinic proceedings Innovations, quality & outcomes. 2019;3(2):200-14.
7. Watkins D, Rosenblatt DS. Inherited defects of cobalamin metabolism In Vitamins and hormones 2022 Jan 1 (Vol. 119, pp. 355-376). Academic Pres
8. Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, Ueland PM. Vitamin B12 deficiency. Nature reviews Disease primers. 2017 Jun 29;3(1):1-20.
9. Coelho D, Suormala T, Stucki M, Lerner-Ellis JP, Rosenblatt DS, Newbold RF, et al. Gene identification for the cblD defect of vitamin B12 metabolism. The New England journal of medicine. 2008;358(14):1454-64.
10. Ahrens-Nicklas RC, Serdaroglu E, Muraresku C, Ficicioglu C. Cobalamin C Disease Missed by Newborn Screening in a Patient with Low Carnitine Level. JIMD reports. 2015;23:71-5.
11. Ahrens-Nicklas RC, Whitaker AM. Efficacy of early treatment in patients with cobalamin C disease identified by newborn screening: a 16-year experience. 2017;19(8):926-35.
12. Almannai M, Marom R, Divin K, Scaglia F, Sutton VR, Craigen WJ, et al. Milder clinical and biochemical phenotypes associated with the c.482G>A (p.Arg161Gln) pathogenic variant in cobalamin C disease: Implications for management and screening. Molecular genetics and metabolism. 2017;122(1-2):60-6.
13. Brooks BP, Thompson AH, Sloan JL, Manoli I, Carrillo-Carrasco N, Zein WM, et al. Ophthalmic Manifestations and Long-Term Visual Outcomes in Patients with Cobalamin C Deficiency. Ophthalmology. 2016;123(3):571-82.
14. Lerner-Ellis JP, Tirone JC, Pawelek PD, Doré C, Atkinson JL, Watkins D, et al. Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. Nature genetics. 2006;38(1):93-
15. Nguyen MG, Tronick L, Modirian F, Mardach R, Besterman AD. Neurodevelopmental and neuropsychiatric disorders in cobalamin C disease: a case report and review of the literature. Molecular Case Studies. 2022 Feb 1;8(2):a006179100.

16. Fischer S, Huemer M, Baumgartner M, Deodato F, Ballhausen D, Boneh A, Burlina AB, Cerone R, Garcia P, Gökçay G, Grünewald S. Clinical presentation and outcome in a series of 88 patients with the cblC defect. Journal of inherited metabolic disease. 2014 Sep;37:831-40.
17. Huemer M, Diodato D, Schwahn B, Schiff M, Bandeira A, Benoist JF, Burlina A, Cerone R, Couce ML, Garcia-Cazorla A, La Marca G. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. Journal of inherited metabolic disease. 2017 Jan;40:21-48.