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CASE SERIES

Intramuscular Vitamin B12 Treatment in Transcobalamin II Deficiency: Case Series Clinical Outcomes

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Background: Transcobalamin II (TC II) deficiency is a rare autosomal recessive disorder that typically manifests in early infancy. Symptoms include failure to thrive, vomiting, weakness, and pancytopenia. If left undiagnosed and untreated, it can be life-threatening. TC II is crucial for transporting cobalamin (vitamin B12), which plays a vital role in homocysteine and methylmalonic acid metabolism. It serves as a cofactor in neurotransmitter synthesis and protein methylation processes.

Methods: In this study, we reviewed the clinical presentation, treatment approaches, and long-term outcomes of four patients with confirmed TC II deficiency. All subjects were born to consanguineous parents and exhibited symptoms between birth and four months of age.

Results: All patients presented with hematological abnormalities, elevated methylmalonic acid (MMA), and increased total homocysteine (tHcy) levels. Whole Exome Sequencing (WES) confirmed TC II deficiency in all cases, revealing diverse mutation spectra, primarily frameshift mutations (leu320Valfs*51, and IIe330Hisfs*9). No clear genotype-phenotype correlations were observed. The majority of patients were treated with intramuscular hydroxocobalamin (OH-Cbl), resulting in clinical and biochemical improvements.

Conclusion: This study underscores the importance of early detection and appropriate management of TC II deficiency to prevent permanent morbidity and potentially fatal outcomes. Regular monitoring of clinical and neurological status, as well as MMA and tHcy levels, is essential to ensure adequate therapy. Intramuscular treatment is the preferred route to prevent neurological deficits and optimal markers normalization.

Keywords: cobalamin, Cbl, vitamin B12, transcobalamin II, hydroxocobalamin, OH-Cbl

Background

Cobalamin (Cbl), commonly known as vitamin B12, plays a vital role in the proper physiological development of various bodily systems. This indispensable nutrient is a key player in hematopoiesis and formation of all major blood components, including erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets).[1] Additionally, Cbl plays a role in the nervous system and in keeping peripheral nerves healthy, as a cofactor in common metabolic pathways important for neurotransmitter synthesis and protein methylation processes.[2] The human body depends on nutrition and dietary intake from sources like meat, eggs, and dairy products to obtain Cbl. A deficiency in consuming Cbl or problems with its absorption can lead to various issues, including macrocytic anemia, weakened immune function, and peripheral neuropathy.[3]

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The absorption process for Cbl begins in the upper part of the digestive system. This process is set in motion by the initial uptake of the vitamin. The absorption is aided by a group of transporter proteins, which are all derived from a single ancestral gene (Figure 1).[4] These proteins have a similar structure, with about 60–80% of their makeup being shared among them.[5] Haptocorrin (HC), formerly known as R-binder or transcobalamin-1, produced by the salivary glands, attaches to Cbl forming Cbl-HC complex, shielding it from the stomach's highly acidic environment. As the reaches the duodenum, it will be released by pancreatic enzymes.[6] Subsequently, Cbl forms a complex with intrinsic factor (IF) encoded by *GIF* gene, a specialized glycoprotein secreted by the parietal cells (also known as oxyntic cells) found in the body and fundus of the stomach and exhibits the strongest affinity for Cbl among its binding proteins.[7] The absorption of Cbl in the terminal ileum is made possible through the formation of a complex between Cbl and IF (IF-Cbl complex) which then recognized and taken up by specialized enterocytes (Figure 1). These enterocytes have a unique receptor complex on their apical surface, known as Cubam, which consists of two proteins: Cubilin (encoded by *CUBN*) and Amnionless (encoded by *AMN*).[8] The Cubam receptor complex binds to the IF-Cbl complex, triggering its endocytosis which allows the enterocytes to internalize the Cbl, effectively and their deficiencies lead to Imerslund-Gräsbeck syndrome (IGS).[9,10]

The next phase involves the transport of Cbl from the enterocytes into the circulatory system for distribution where it is primarily transported by a protein called Transcobalamin II (TC II). Unlike other protein transporters, TC II is unique in that it lacks glycosylation. It is synthesized by vascular endothelial cells and is encoded by the *TCN2* gene.[11] TC II plays a crucial role in distributing Cbl throughout the body to all cells. It forms a strong and specific bond with Cbl, creating what is known as the holo transcobalamin complex (holoTC). This binding affinity is significantly higher than that of HC, another Cbl-binding protein. The holoTC complex represents the biologically active form of vitamin B12 in

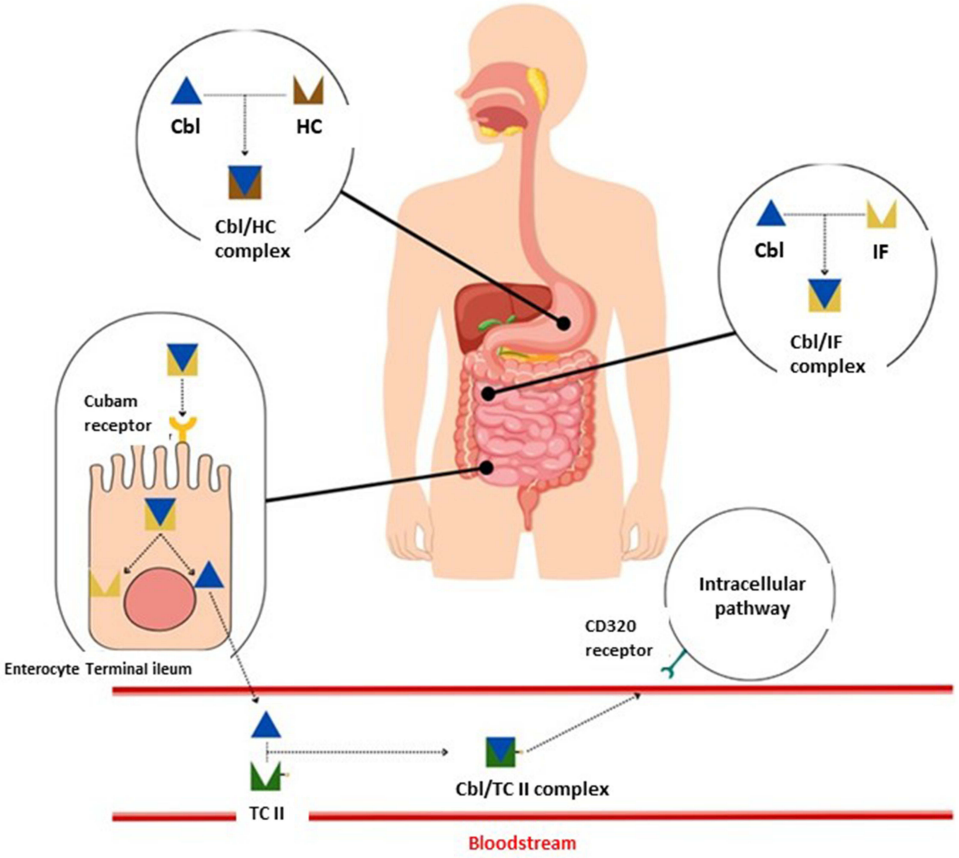

Figure 1 The figure shows the Extracellular Pathway. Ingestion, absorption, transportation into the bloodstream, and cellular uptake.
Abbreviations: Cbl, Cobalamin; HC, Haptocorrin; IF, intrinsic factor; TC II, Transcobalamin.

the body.[6] TC II deficiency is a rare genetic disorder that typically manifests in newborns or young infant. This condition stems from mutations in the *TCN2* gene, located on chromosome 22q12.2, which disrupt the cellular absorption of Cbl.[12] The disorder is manifested as megaloblastic anemia, failure to thrive, gastrointestinal issues (vomiting, diarrhea), increased susceptibility to infections and neurological symptoms.[13]

Currently, there is a lack of established protocols for managing TC II deficiency. Specifically, there are no standardized recommendations concerning the best approach the treatment of TC II deficiency. Herein, we review the literature and report 4 cases of TC II deficiency. In this study our focus is on the management outcome and on the markers that are used to monitor and assess the response to treatment.

Materials and Methods

Patient Data

A retrospective chart review was conducted on pediatric patients with confirmed diagnosis of TC II deficiency with homozygous mutations in *TCN2* gene during the period January 2010 to December 2024 at two tertiary care centers in Riyadh, Saudi Arabia: King Abdulaziz Medical City and King Fahad Medical City. Clinical, laboratory, and genetic data pertinent to the diagnosis of TC II deficiency were extracted from the medical records by collaborating physicians at the participating institutions. The patients with missing or incomplete data were excluded (3 cases). The study protocol was reviewed and approved by the Institutional Review Board of the King Abdullah International Medical Research Centre (KAIMRC), with the assigned IRB number NRR24/017/12. The Parents of the participating patients gave informed consent for the publication of the case details and any accompanying images.

Results

This study presents a cohort of 4 patients with confirmed TC II deficiency (Table 1). All patients were offspring of consanguineous unions and presented during infancy, with onset ranging from birth to 4 months of age. The gender distribution was 75% male (n=3) and 25% female (n=1). One set of siblings was identified: cases 1 and 2. The predominant clinical manifestations included pyrexia, gastrointestinal disturbances (diarrhea and emesis), reduced oral intake, and failure to thrive. Hematological analysis revealed pancytopenia in all patients in this cohort (Table 1), with a majority exhibiting elevated serum methylmalonic acid levels. Therapeutic intervention consisted of intramuscular cobalamin administration for all patients, some of whom received additional oral supplementation.

Molecular

All patients diagnosed with TC II deficiency that was confirmed by molecular testing. Using Whole Exome Sequencing (WES), a homozygous pathogenic and probable pathogenic in the *TCN2* gene was detected in all patients. The first two cases had "homozygous VUS in TCN2 gene, c.64+4A>T", the 3rd case had "homozygous likely pathogenic variant; c.987dup p.(IIe330Hisfs*9)", the 4th case had homozygous pathogenic mutation; c.926_927dup, p.(leu320Valfs*51) (Table 1).

Case 1

The first case an 18-year-old girl, with a complex medical history dating back to early infancy. At 6 weeks of age, she presented with intrauterine growth restriction, recurrent infections, gastrointestinal symptoms including diarrhea and vomiting, and severe pancytopenia necessitating substantial blood product transfusions. Initial treatment consisted of intramuscular cyanocobalamin (CN-Cbl) at a dose of 1 mg weekly.

At age 14, the therapeutic regimen was modified to include intramuscular hydroxocobalamin (OH-Cbl) injections of 1 mg weekly, supplemented with 10 mg of oral OH-Cbl. Laboratory findings consistently demonstrated leukopenia with neutropenia and hypogammaglobulinemia, specifically low IgM levels. The patient's history was notable for poor adherence to treatment, resulting in elevated methylmalonic acid (MMA) levels. Subsequently, the treatment protocol was intensified to three times weekly intramuscular injections combined with 10 mg of oral OH-Cbl. At present, the patient is 18 years old, exhibits no developmental delays, demonstrates satisfactory academic performance, and has matriculated into a collegiate program.

Table 1 Clinical, Laboratory, and Molecular Information of Cases

Case	Age/Gender	Age of Onset	Symptoms of Presentation	Laboratory Investigations at Presentation			Mutation	Treatment Method	Laboratory Investigations After Treatment			Clinical Outcome
				Pancytopenia	MMA nmol/L	tHcy µmol/L			Pancytopenia	MMA nmol/L	tHcy µmol/L	
Case 1	18 years, Male	6 weeks	Growth restriction, recurrent infections, fever, diarrhea, vomiting.	Yes	790	7.2	Homozygous VUS variant in *TCN2* gene, c.64 +4A>T	1mg CN-Cbl IM weekly → OH-Cbl at age of 14 years → increased to 3/ week with 10mg orally OH-Cbl daily	Corrected	181.2	5.9	Normal growth and development
Case 2	11 years, Male	45 days	Fever, lethargy, sepsis	Yes	5300	25.4	Homozygous VUS variant in *TCN2* gene, c.64 +4A>T	10mg OH-Cbl oral daily → IM OH-Cbl 1/wk. → increased to 3/week with 10mg orally OH-Cbl daily	Corrected	118.4	3.4	Motor and speech delay, Hyperlaxity of the joints, Hypotonia, lack of coordination of movements, and unsteady gait
Case 3	4 years, Male	3 months	Failure to Thrive, Head lag, generalized hypotonia	Yes	1332.3	22.2	Homozygous likely pathogenic variant in *TCN2* gene, c.987dup p. (Ile330Hisfs*9)	1mg OH-Cbl IM weekly	Corrected	140.9	5.8	Mild speech delay
Case 4	8 years, Female	4 months	Mildly distended abdomen, Sepsis, URTI, Hypotonia and dysphagia	Yes	792	ND	Homozygous pathogenic variant in *TCN2* gene, c.926_927dup,p. (leu320Valfs*51)	1mg IM CN-Cbl 3/week	Corrected	51	ND	Normal growth and development

Abbreviations: ND, Not done; MMA, Methylmalonic Acid; tHcy, Total homocysteine; VUS, Variant of unknown significant; CN-Cbl, Cyanocobalamin; OH-Cbl, Hydroxocobalamin; IM, Intramuscular; URTI, Upper respiratory tract infection.

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Case 2

An 11-year-old male patient initially presented in the neonatal period with symptoms including emesis, apneic episodes, and clinical features suggestive of neonatal sepsis accompanied by neutropenia. Due to the persistence of neutropenia, a comprehensive hematological evaluation was conducted, leading to the diagnosis of TC II deficiency. Following diagnosis, the patient was initially managed with 10 mg of oral OH-Cbl. Despite initial improvements in clinical status and hematological parameters, the patient exhibited developmental concerns at 19 months of age, including speech delay, hypotonia, ataxia, and impaired coordination. Neuroimaging via brain MRI revealed cerebellar atrophy.

At 3 years of age, the patient was referred for mental health evaluation, which identified developmental delays, particularly in motor skills and speech, as well as a lack of bladder control. The treatment regimen was modified to weekly intramuscular injections of 1 mg OH-Cbl.At 7 years of age, the therapeutic approach was augmented by adding 10 mg of oral OH-Cbl daily to the existing intramuscular regimen. Despite these interventions, the patient continued to exhibit poor concentration and academic performance, necessitating an increase in intramuscular injection frequency to twice weekly, and subsequently to three times weekly. Currently, the patient presents with persistent motor and speech delays, with no significant improvement in neurological symptoms. The patient's educational needs are being addressed through placement in special education classes.

Case 3

A 4-year-old male patient initially presented at 3 months of age with upper respiratory tract infection (URTI) symptoms, fever, and right upper lobe pneumonia requiring oxygen support. The patient underwent extensive investigation due to pancytopenia, which revealed significant hematological abnormalities. Complete blood count showed leukopenia (WBC: 2.75/L), anemia (RBC: 2.63/L), thrombocytopenia (Platelets: 11/L), and elevated reticulocyte count (Retic Corrected: 5.69). Peripheral blood smear analysis demonstrated moderate pancytopenia and neutropenia with hypersegmented neutrophils. Bone marrow aspiration revealed reduced megakaryocytes, hypersegmented and vacuolated granulocytes, consistent with the pancytopenia. The patient required multiple blood transfusions and one platelet transfusion.

Immunological, infectious disease, and metabolic screening investigations were unremarkable. However, serum MMA was markedly elevated at 28245.8 (normal 0–389 nmol/L), and homocysteine (Hcy) was elevated at 22.2 (normal 5.0–16.2 μmol/L). A therapeutic trial of daily intramuscular OH-Cbl (1 mg) was initiated, with plans to reassess MMA and total homocysteine (tHcy) levels after two weeks. Genetic testing confirmed the diagnosis of TC II deficiency. Following approximately two years of stable condition, normal growth and development, and acceptable MMA and tHcy levels, a trial of monthly intramuscular OH-Cbl administration was attempted with close monitoring. After three months of monthly injections, there was an upward trend in MMA and Hcy levels, and a downward trend in Cbl levels, although no clinical manifestations were observed. Consequently, the treatment regimen was adjusted to biweekly intramuscular injections. Due to persistently elevated MMA levels, the frequency was further increased to weekly administrations. Currently, at 4 years of age, the patient receives 1 mg of intramuscular OH-Cbl weekly. His developmental milestones are age-appropriate, with the exception of mild speech delay, which may be attributed to chronic otitis media.

Case 4

An 8-year-old girl presented at age of 4 months of age with sepsis like picture, associated with lethargy, poor oral intake and pharyngeal dysphagia, and mild hypotonia. On Investigations she had pancytopenia (RBC: 3.65, Hgb: 10.93, WBC: 4.75), serum Cbl level was within normal limits. However, serum MMA was elevated (792nmol/L). Urine organic acids detected MMA. TC II deficiency was suspected, and she was started on intramuscular CN-Cbl 1mg twice/weekly and hematological markers improved (RBC: 4.22, Hgb: 12.6, WBC: 6.47) Serum MMA after treatment was 51. Currently she is without any long-term complications, including neurological symptoms.

Discussion

TC II Deficiency usually presents in the first few months of life with failure to thrive, gastrointestinal symptoms such as oral ulcers and diarrhea, recurrent infections, pancytopenia, and neurological symptoms. The disease should be suspected in such presentation and should be treated as early as possible despite normal serum cobalamin levels may appear

normal, as holoTC represents only about 20% of total cobalamin, while elevated levels of MMA and tHcy in blood and urine are indicative of the condition, the diagnosis of TC II deficiency is need to be confirmed by genetic analysis.[14] Interestingly, The N-terminal region of the TC receptor CD320 (also known as TCblR/CD320) serves as a binding site for HoloTC. This interaction initiates a process of endocytosis, where the bound complex is internalized into a vesicle. Subsequently, this vesicle merges with lysosomes, leading to two outcomes: the release of free Cobalamin (Cbl) into the cytoplasm and the breakdown of TC II.TCblR/CD320 is widely distributed throughout most body tissues.[15]

The clinical presentations of our patients aligned closely with those described in existing literature. These patients demonstrated near-normal outcomes. In contrast, one patient (Case 2) initially treated with oral cobalamin supplementation for 3 years before transitioning to intramuscular administration developed neurological sequelae. This case series highlights the importance of early recognition and appropriate management of TC II deficiency, emphasizing the potential superiority of intramuscular Cbl administration over oral supplementation in preventing neurological complications. We initiated Cbl supplementation using various forms and administration dosages, which led to diverse outcomes. Notably, all cases in this study treated via the intramuscular route exhibited normal neurological development. Cases 1 and 2 shared the same genetic mutation but received different treatments. Case 2 was administered 10mg of oral OH-Cbl daily if the first few years of life. Unfortunately, this patient developed multiple neurological symptoms, including ataxic gait, speech deficits, and impaired movement coordination. Furthermore, brain MRI revealed evidence of cerebellar involvement. Following a change in therapy to intramuscular injections three times per week, combined with 10mg of oral OH-Cbl, the patient's neurological symptoms have stabilized. Multiple studies have documented the emergence of neurological symptoms and/or retinopathies in patients treated with oral OH-Cbl over extended periods. Some reports indicate improvement when transitioning to the intramuscular route, once weekly as minimum may yield more favorable outcomes.[16–18]

The treatment frequency and dosage varied among the cases: case 3, initially received 1 mg intramuscular injections weekly. When the frequency was reduced, MMA levels increased (Figure 2), though no symptoms developed. Case 1, Started with 1mg intramuscular weekly, then increased to 1mg three times per week, along with oral OH-Cbl. This increase occurred despite normal functioning and good academic performance. Case 2, was shifted to 1mg intramuscular three times weekly plus oral OH-Cbl, after being initially managed with 10mg of oral OH-Cbl, but showed no neurological improvement

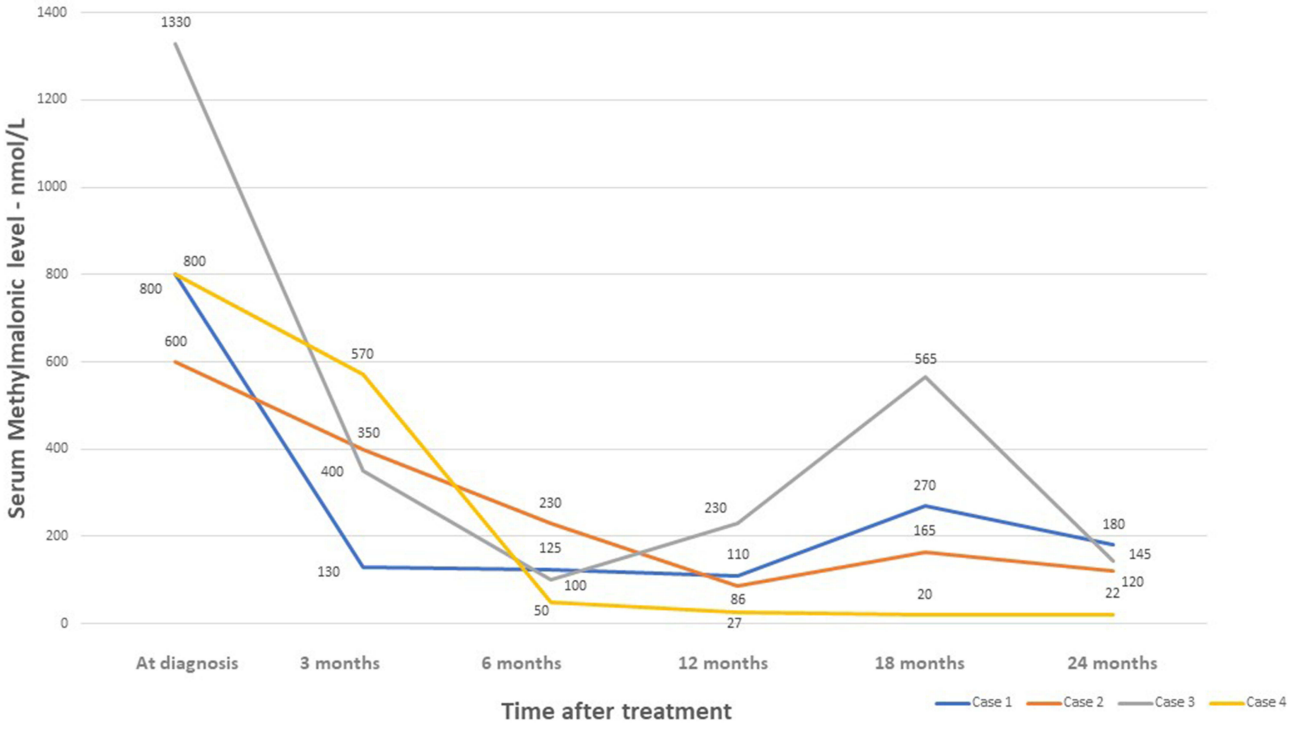

Figure 2 The figure shows the metabolite levels of TC II patients (all cases). Serial serum Methylmalonic Acid levels (MMA) at diagnosis and after treatment.

despite normal biochemical and hematological markers. Regarding the form of Cbl used, our patients showed no difference in outcomes, where both patients receiving intramuscular CN-Cbl or intramuscular OH-Cbl experienced favorable outcomes without neurological symptoms. However, literature suggests that CN-Cbl is associated with a higher rate of long-term complications compared to OH-Cbl.[19,20] Furthermore, a case study described a patient who had been receiving intramuscular CN-Cbl 1mg every 10 days since 7 months of age. This patient developed neurological symptoms at 13 years old and was diagnosed with retinal dystrophy at 16 years old. Upon switching to intramuscular OH-Cbl 5mg three times per week, the patient's neurological signs improved, and there was no progression of retinal degeneration by 19 years of age.[16] The variability in outcomes may be linked to the treatment frequency, nevertheless, all patients began receiving intramuscular OH-Cbl at an early age, with the dosage ultimately reaching 1 mg weekly. This regimen resulted in improved hematological and neurological markers. Consequently, OH-Cbl is considered preferable to CN-Cbl.[19] When monitoring patients, it's important to note that hematological markers can occasionally be misleading. Patients may experience complications even when their CBC and tHcy levels appear normal. This phenomenon was clearly demonstrated in (Case 2), where the patient exhibited normal CBC and mean corpuscular volume (MCV) while receiving oral OH-Cbl supplementation (Table 1). Despite these seemingly normal results, the patient subsequently developed persistent cerebellar symptoms that did not resolve.[21] Patients should undergo regular monitoring, which includes: assessment of hematological markers, measurement of MMA and tHcy levels, comprehensive neurological examinations. Additionally, for long-term follow-up, ophthalmological evaluations may be advisable.

In conclusion, Transcobalamin II (TC II) deficiency poses a potentially life-threatening risk if not promptly identified and treated and may result in lasting morbidity. Regular monitoring of clinical and neurological status, as well as biochemical markers is crucial for ensuring optimal therapeutic outcomes. Furthermore, there is a pressing need for additional prospective research that focuses on refining treatment protocols in specific intramuscular OH-Cbl vs intramuscular CN-Cbl and evaluating long-term outcomes in patients with TC II deficiency.

Ethics Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. This study was approved by King Abdullah International Medical Research Center IRB (IRB Number: NRR24/017/12).

Informed Consent

The Parents of the participating patients gave informed consent for the publication of the case details and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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