Long-term Outcome of a Patient With Transcobalamin Deficiency Caused by Tcn2 Mutation: A Case Report

Francesco Martino (francesco.martino@uniroma1.it)
Universita degli Studi di Roma La Sapienza Facolta di Medicina e Odontoiatria
Alessandra Magenta
"Consiglio Nazionale delle Ricerche"
Maria Letizia Troccoli
Ospedale Sant'Andrea
Eliana Martino
Universita degli Studi di Roma La Sapienza Facolta di Medicina e Odontoiatria
Concetta Torromeo
Universita degli Studi di Roma La Sapienza Facolta di Medicina e Odontoiatria
Paolo Versacci
Universita degli Studi di Roma La Sapienza Facolta di Medicina e Odontoiatria
Francesco Barillà
Universita degli Studi di Roma La Sapienza Facolta di Medicina e Odontoiatria

Case report

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Abstract

Background:Transcobalamin deficiency is a rare autosomal recessive inborn error of cobalamin transport (prevalence: <1/1000000)whichclinically manifests in early infancy. Case presentation:We describe the case of a 30 year old woman who at the age of 30 days presented with the classical clinical and laboratory signs of an inborn error of vitamin B_{12} metabolism. Family history revealed a sister who died at the age of 3 months with a similar clinical syndrome and with pancytopenia.Shewas started on empirical intramuscular (IM) cobalamin supplements (injections of hydroxocobalamin 1 mg/day for 1 week and then 1 mg twice a week) and several transfusions of washed and concentrated red blood cells.With thesetreatments a clear improvement in symptoms was observed, with the disappearance of vomiting, diarrhea and normalization of the full blood count.At 8 years of age injections were stopped for 3 monthscausing the reappearance of megaloblastic anemia.IM hydroxocobalamin was then restarted*sine die*.The definitive diagnosis could only be established at 29 years of age when a genetic evaluation revealed homozygous nonsense variation in exon 8 of the TCN2 gene.Currently she is a 30-year old healthy lady taking 1 mg of IM hydroxocobalamin once a week.

Conclusions: Our case report highlights that early detection of TC deficiency and early initiation of aggressive IM treatment is likely associated with disease control and an overall favorable outcome.

Background

VitaminB_{12} (B_{12}) also known as cobalamin is absorbed at the terminal ileum level, associated with a glycoprotein of gastric origin (intrinsic factor), by means of an endocytosis mechanism, mediated by an enterocyte membrane receptor (1).Subsequently the B_{12} is secreted in the bloodstream where it binds to the vector protein haptocorrin (HC),(previously named transcobalamin I).In the enterocyte, the IF-Clb complex dissociates and Cbl reaches the portal circulation where it is bound to transcobalamin (formerly known as transcobalamin II [TC]) (1). In this bound form it is recognized by the surface receptors of the user cells (mainly those of the labile tissues with proliferative activities such as those of the bone marrow and of the germinative layer of the epithelia) and introduced, through a process of micropinocytosis, inside the cell, where the B_{12} is freed from the vector by lysosomal acid hydrolases and reduced by cytoplasmic enzymes(2).

At this point the reduced B_{12} undergoes two separate metabolic processes to be converted into the two co-enzymatically active forms:

- • in the cytosol, in the form of methyl-cobalamin, it becomes part of the catalytic process of the enzyme methionine synthase;
- • in the mitochondrion undergoes an adenosylation process that forms adenosyl-cobalamin (coenzyme of methylmalonyl-CoA mutase).

Congenital errors of cobalamin metabolism can affect any stage of absorption, blood transport and intracellular use.

The only congenital absorption deficit is due to a genetic alteration of the enterocytic receptor (Imers Lund syndrome), which is characterized by low serum cobalamin levels, a normal intrinsic factor and megaloblasticanemia(3).

TC deficiency, is a typical transport error characterized by megaloblasticanemia with normal serum levels of B_{12}(4).

In this form there is a combined deficiency of synthesis of both methylcobalamin (methionine synthase coenzyme) and adenosyl cobalamin (methylmalonyl-CoAmutase coenzyme), with the consequent possibility of homocystinuria and methylmalonic aciduria. A massive homocystinuria with methylmalonicaciduria is characteristic of the combined deficits of the common intracellular metabolism of the B_{12}(5).

Isolated deficiencies of the specific metabolic pathways of adenosylcobalamin and methylcobalamin lead, respectively, to methylmalonicaciduria and homocystinuria. In the first case there will be the forms of methylmalonic acidemia due to coenzyme deficiency, which respond in part to therapy with B_{12}(ca. 10–20%), while the methylcobalamin deficiency blocks the methylation of homocysteinethus causing massive homocystinuria(6). The activity of methionine synthetase also requires the presence of some intermediates of the folate metabolism. However, congenital disorders of folate metabolism exist which, by altering the correct synthesis of these intermediates, cause a deficiency of enzymatic activity.

In particular, in 5–10,methylentetrahydrofolate reductase deficit, there is a lack of synthesis of 5 methyltetrahydrofolate which is the direct donor of the methyl group to homocysteine for the synthesis of methionine (7).

The blockade of methionine synthetase activity causes massive homocystinuria but megaloblastic anemia has never been found.

As for B_{12} there is also a folate malabsorption which is characterized by severe megaloblasticanemia with very low serum folate levels. Albeit rare there are also congenital disorders of folate metabolism, such as the functional deficit of dihydrofolatereductase and the cellular uptake defect of folate, characterized by severe megaloblasticanemia and pancytopenia.These disorders are sensitive to therapy with folate at high doses, in case of normal serum levels of folic acid. In the few cases described it is not clear whether the pathogenesis is due to a primitive metabolic deficit of folate; in any case, aminoaciduria has never been found.

Bloodcobalamin levels are not usually low because the majority of serum cobalaminis bound to HC and not to TC.

TC deficiency (OMIM #275350) is a rare autosomal recessive disorder: the most frequent mutations are deletions or insertions inthe TCN2 gene, resulting in frame shifts that predict proteintruncation(8, 9). Nonsense mutations and point mutations that activate exonic cryptic splice siteshave also been reported (10, 11), as well as, polymorphic variants have also been described(8, 11).

Case Description

I.V. was born to Italian non consanguineous parents on the 23rd October of 1990.She was first evaluated at theage of 30 days when she presented with recurrent vomiting with every meal (exclusive breast feed), diarrhea and weight loss (< 25% percentile). She was born from eutocic birth with a weight of 3,300 g (50th percentile), head circumference 34.5 cm (50th percentile), length 50 cm (50th percentile).

Family history revealed a sister who died at the age of 3 months with a similar clinical syndrome and with pancytopenia. This sibling was diagnosed an acute myeloid leukemia, but the diagnosis was not confirmed at post-mortem examination.

On admission to the hospital our patient showed pallor, recurrent vomiting at every meal, diarrhea but clinical examination, including neurological evaluation, was otherwise normal.

Complete blood count (CBC) revealed megaloblastic anemia with leukopenia as reported in Table 1.

Table 1
Blood Tests

Red Blood Cell Count (RBC)	**2,040,000/µL**
Hemoglobin (Hb)	7.5 g/dL
Hematocrit (Ht)	23.5%
Mean Corpuscular Volume (MCV)	115.2 fL
Mean Corpuscular Hb (MCH)	36.8 pg/cell
MCH concentration (MCHC)	31.9 g/dL
White Blood Cell Count (WBC)	5400/µL
-neutrophils	12%
-lymphocytes	83%
-monocytes	5%
-platelet count	165,000/µL

Peripheral blood film showed hypochromic macrocytic Red Blood Cells (RBC) and hyper-segmented neutrophils, with no reticulocytosis. Folate and cobalamin blood concentrations were normal

(19.2 mg/mL and 1940 pg/mL respectively). Urinary spot methylmalonic acid (qualitative) was not elevated, while homocystinuria was present.

The clinicalpicture,includingfamily history, and laboratory findings suggested the diagnostic suspect of a methylation deficiency of B_{12}.

Treatment was started with several transfusions of washed and concentrated RBC and intramuscular (IM) injections of hydroxocobalamin (1 mg/day for 1 week and then 1 mg twice a week).The clinical picture progressively improved with disappearance of vomiting and diarrhea, normalizationof blood tests and body growth.

When she was 8 years old an attempt to suspend treatment for three months was unsuccessful causing the reappearance of megaloblastic anemia. IMhydroxocobalamin needed to be restarted*sine die*. Menarche started at the age of 10 years and half. In the last pediatric examination at the age of 16 years, normal growth and development were observed (weight 50 kg, height 150 cm, body mass index 21.65). Cardiovascular and neurological examinations, including ECG and EEG, were normal. Dual-energy X-ray absorptiometry was within normal limits. Blood tests showed a persistent normalization of the CBC and related indices: RBC 4,570,000/μL, Hb 14.8 g/dL, MCV 88 fL, WBC 6,600/μL, platelets 261,000/μL.

At present time in 2020 she is a 30-year old healthy lady taking 1 mg of IM hydroxocobalamin once a week (Table 2).

Table 2
Timeline

Age	Symptoms	Blood Analysis	Diagnosis	Treatment	Outcome
30 days	-Pallor -Recurrent vomiting at every meal -Diarrhea -Weight loss (< 25th percentile)	-Megaloblastic anemia -Normal Folate and cobalamin blood concentrations -Urinary spot methylmalonic acid normal homocystinuria present	At 45 day a suspected transcobalamin 2 deficiency was diagnosed	Several transfusions of washed and concentrated RBC and IM injections of hydroxocobalamin (1 mg/day for one weeks and thereafter 1 mg/ twice a week)	-Vomiting and diarrhea disappearance -Blood test normalization -Body growth normalization
11 months	Any symptoms	-Normal hematological picture		IM injections of 1 mg/week of hydroxocobalamin	-Excellent health -Body weight (between the 50th and 75th percentiles)
8 years	Any symptoms	-Normal hematological picture		Therapy suspension for three months	Megaloblastic anemia reappearance
8 years	Any symptoms	-Megaloblastic anemia		Therapy resumption IM injections of 1 mg/week of hydroxocobalamin	Hematological picture normalization
10 years and half	Appearence of menarche				
29 years	Any symptoms	-Normal hematological picture	Genetic confirmation of TCN2 mutation	IM injections of 1 mg/week of hydroxocobalamin	Good health
At present	Any symptoms	-Normal hematological picture		IM injections of 1 mg/week of hydroxocobalamin	She is a 30 years old healthy lady

At 29 years of age the patient underwent definitive genetic diagnosis and therefore weanalysed the sequence of the gene TCN2 (NM_000355.3). We found a c.1114_1115delAC deletion in homozygosity at

the exon 8 level, which determines a frameshift or slippage of the reading module, with consequent incorrect translation of TC protein. The wild type (*wt*) TC protein is 427aa long, the mutated protein has the identical amonoacidic (aa) sequence until 372aa and then introduces 37aadifferent from *wt* protein, and a stop codon that truncated the protein at 409aa (Fig. 1).

We also found a single nucleotide variant in homozygosity A > G in the first exon region (rs2240433).

Diagnostic Assessment

Blood count, RBC indexes and biochemistry were performed by routine methods. Serum was frozen following centrifugation and thawed for further studies. TCN2 of the gene sequence analysis was performed by Genechron S.r.l.

Folate, methylmalonic acid blood concentrations and homocystinuria were evaluated using standard procedures.

B_{12} was measured by radio-immunoassay, and B_{12} absorption was evaluated by the Schilling test with 1 mg of B_{12}.

Discussion And Conclusion

TC deficiency is a rare and lethal autosomal recessive disease with an early infantile onsetand the following clinical and laboratory features: failure to thrive, weakness, diarrhoea, pallor, anemia, pancytopenia,a gamma globulinemia.

Thissyndrome may resemble a neonatal leukemia or a severe combined immunodeficiency disease(12, 13). Differential diagnosis with these two disease should be warranted because TC deficiency, when treated aggressively, appears to be associated with an overall favorable outcome.

TC deficiency patients usually present with megaloblastic anemia of variable severity. A delay in diagnosis andtreatmentare associated with life threatening neurological and hematopoietic complications, which can also be fatal(13, 14).

Patients might show isolated elevation in methylmalonicaciduria (MMA), whereas others show combined increase in circulating MMA and homocysteine(15).

In our patient there was a family history of a similar syndromethat included pancytopenia. The blood concentrations of folate and cobalamin were normal excluding deficits where they are low (deficiency of the absorption of B_{12}, malabsorption of folate). Aminoaciduria highlighted the presence of homocysteine and the absence of methylmalonic acid, leading to the exclusion of a deficiency of methylmalonyl-CoAmutase. These findings and anemia lead to the diagnostic suspicion of a methionine synthase deficiency since methylcobalamin is the coenzyme involved in homocysteine transformation into

methionine(16, 17).The diagnostic suspicion was indirectly confirmed by the clear response to empiric treatment with IM hydroxycobalamin: disappearance of vomiting, diarrhea and normalization of the hematologicalpicture.

At present there are no guidelines on the treatmentof TC deficiency regarding to the form to use(i.e. hydroxocobalamin*vs*cyanocobalamin), the dose, the administration method (IM*vs* oral),the frequency (weekly *vs* monthly) and the duration of administration, the treatment monitoring period and follow-up.

IM administration of 1 mg of hydroxocobalamin or cyanocobalamin once a week for a lifetime appears to be the most suitable treatment regime according to the observational data reported in a series of 30 patients(13).

The working hypothesis that such a treatment regime can be correct is confirmed*ex adiuvantibus* in our patient by the observed reappearance of megaloblastic anemia following the attempted suspension of IM hydroxycobalaminat 8 years of age. The timely resumption of treatment (3 mg in the first week, 2 mg in the second week and subsequently 1 mg per week *sine die*) normalized the hematological picture.

In conclusion our case report highlights that early detection of TC deficiency and early initiation of aggressive IM treatment is likely associated with disease control and an overall favorable outcome.

Genetic counseling should be provided to affected families. Neonatal screening could be useful in the early diagnosis of the syndrome:some studies suggest that prenatal diagnosis of TC deficiency is possible by means of measuring TC production in amniotic-fluid cells (18–21).

Patient Perspective

The treatment is easily administered, does not give adverse events and overall is well tolerated and safe.

Declarations

Ethical Approval and Consent to partecipate

The parents and the patient (at the age of 29) signed an informed consent for treatment.

Consent for publication

The patient (at the age of 29) signed an informed consent for the publication of data.

Availability of Data and Materials

The data and materials generated and/or analyzed during the current study are available from the

corresponding author on reasonable request.

Competing interest

The authors declare no conflict of interest

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Authors' contributions

Diagnosis and treatment: FM; Cinical checks during follow-up: FM, EM,CT, PV. Conceptualization: FM, AM, FB. Writing, Review & Editing: FM, AM, MLT, FB. All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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This manuscript is dedicated to the memory of Prof. Omero Giardini

Authors' information

[1]Department of Pediatrics Gynecology and Obstetrics, Sapienza University of Rome,Viale Regina Elena 324, 00161 Rome, Italy

[2]National Research Council of Italy (CNR), Institute of Translational Pharmacology IFT, Via Fosso del Cavaliere 100, 00133, Rome, Italy.

[3]Clinical Analysis and BiochemistryLaboratory, Sant'Andrea Hospital, Via di Grottarossa, 1035/1039,00189, Rome, Italy

[4]Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, Sapienza University of Rome, VialedelPoliclinico 155, 00161 Rome, Italy

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Figures

TC protein wilde type

427aa

MRHLGAFLFLLGVLGALTEMCEIPEMDSHLVEKLGQHLLPWMDRLSLEHLNPSIYVGLRLSSLQAGTKEDLYLHSLKLGY
QQCLLGSAFSEDDGDCQGKPSMGQLALYLLALRANCEFVRGHKGDRLVSQLKWFLEDEKRAIGHDHKGHPHTSYYQYGLG
ILALCLHQKRVHDSVVDKLLYAVEPFHQGHHSVDTAAMAGLAFTCLKRSNFNPGRRQRITMAIRTVREEILKAQTPEGHF
GNVYSTPLALQFLMTSPMRGAELGTACLKARVALLASLQDGAFQNALMISQLLPVLNHKTYIDLIFPDCLAPRVMLEPAA
ETIPQTQEIISVTLQVLSLLPPYRQSISVLAGSTVEDVLKKAHELGGFTYETQASLSGPYLTSVMGKAAGEREFWQLLRD
PNTPLLQGIADYRPKDGETIELRLVSW

TC protein mutated c.1114_1115delAC

409aa

MRHLGAFLFLLGVLGALTEMCEIPEMDSHLVEKLGQHLLPWMDRLSLEHLNPSIYVGLRLSSLQAGTKEDLYLHSLKLGY
QQCLLGSAFSEDDGDCQGKPSMGQLALYLLALRANCEFVRGHKGDRLVSQLKWFLEDEKRAIGHDHKGHPHTSYYQYGLG
ILALCLHQKRVHDSVVDKLLYAVEPFHQGHHSVDTAAMAGLAFTCLKRSNFNPGRRQRITMAIRTVREEILKAQTPEGHF
GNVYSTPLALQFLMTSPMRGAELGTACLKARVALLASLQDGAFQNALMISQLLPVLNHKTYIDLIFPDCLAPRVMLEPAA
ETIPQTQEIISVTLQVLSLLPPYRQSISVLAGSTVEDVLKKAHELGGFTYETGLLVRPLLNLRDGESGRRKGVLAASPRP
QHPTVARYC-***Stop***-LQTQGWRNH-***Stop***-AEAG-***Stop***-LV

Figure 1

Comparison between TC wild type and mutated protein. The wt protein and the mutated one are identical for the first 372aa (highlighted in bold). Then the mutated protein introduces 37aa different from the wt and a stop codon that truncated the protein.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklistTCN2.pdf