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Transcobalamin II Deficiency in an Infant with a Novel Mutation

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Cobalamin (vitamin B12) is essential for 2 reactions in humans; methylmalonyl-CoA isomerization and methylation of homocysteine. The second reaction is sustained by a cobalamin-dependent enzyme called methionine synthase, which catalyzes the regeneration of an essential amino acid methionine from homocysteine and produces S-adenosylmethionine, the most important cellular methyl-donor. Folate-dependent 1-carbon transferring interconnects with this reaction for de novo purine and thymidylate synthesis. The purines and thymidine are building blocks of deoxyribonucleotides and ribonucleotides.[1-4]

Cobalamin deficiency results in hematological and neurological effects, ranging from milder findings such as weakness and behavioral changes to severe manifestations like pancytopenia and degeneration of the spinal cord. Cobalamin deficiency is a common cause of pancytopenia in infants. Inborn errors of cobalamin transport and metabolism, mainly hereditary transcobalamin II (TC) deficiency, should be investigated in non-nutritional deficiencies in infants.[1,2]

A 65-day-old refugee girl presented with severe cough, fever, and poor feeding. In her history, she was born at 39th gestation week with a 2900 g birth weight and was the first child born from the mother's first pregnancy. Her parents were not relatives. In the ER, there was moderate respiratory distress with tachypnea, tachycardia, pallor, and mild hepatomegaly in physical examination. In addition, the failure to thrive was also noticeable and no dysmorphic appearance was detected. Chest graphy was conformed with bronchopneumonia and she was hospitalized for treatment.

Initial laboratory investigations showed pancytopenic results that hemoglobin was 5.1 g/dL (mean corpuscular volume [MCV] 98 fL), the white cell count was 1180/μL with an absolute neutrophil count of 120/μL, and the platelet count was 11 000/μL. The absolute reticulocyte count was 10 000/μL. Periphery blood smear revealed round enlarged red cells with marked anisocytosis, hypersegmented neutrophils, and thrombocytopenia. Liver and renal function tests were in the normal range for age. Serum electrolyte levels were normal.

Bone marrow aspiration was done to examine erythroid, myeloid, and megakaryocytic morphology and look for other atypical cells like blasts. There were megaloblastic changes and vacuolization in myeloid and erythroid lineages (Figure 1). Serum homocysteine, vitamin B12, and folic aside levels were 35.5 μmol/L (normal range 6-15), 412 pg/mL (normal range 200-860), and 19.9 ng/mL (normal range 2.7-17), respectively. Urine methylmalonic acid was negative, also urine analysis revealed normal. A possible diagnosis of TC deficiency was suspected when the patient was analyzed with history, physical examination, laboratory findings, and literature review. Mutation analyses of the *TCN2* gene were planned with next-generation sequencing.

The intramuscular hydroxocobalamin treatment was given as 1 mg weekly due to probable TC deficiency. The hematologic improvement was observed in a short time. The mutation analysis (homozygous c.22_31del frameshift mutation in *TCN2* gene) confirmed the diagnosis of TC deficiency. Also, this mutation is a novel variant.

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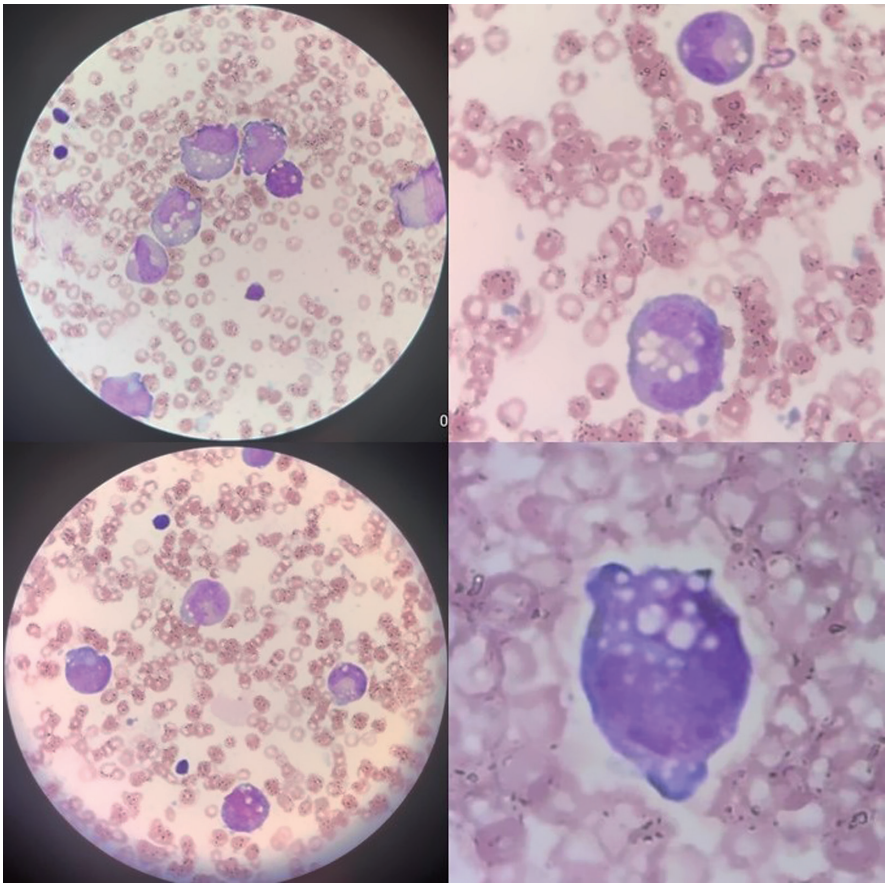

Figure 1. Megaloblastic erythroid and myeloid precursors are demonstrated in the bone marrow aspirate smear. Also, cytoplasmic vacolization is seen in the cells.

The etiologies of cobalamin deficiency are divided into 4 categories: inadequate uptake, defective absorption, defective transport, and defective metabolism. Transcobalamins are carrier proteins of cobalamin; haptocorrin (transcobalamin I or R factor) which is secreted by the salivary glands, binds to protect cobalamin from the stomach acidity and transcobalamin II transports cobalamin to the tissues.[3,5]

Twelve different inborn errors influence intestinal cobalamin absorption, convey of cobalamin in blood, uptake of cobalamin by tissues, or intracellular cobalamin metabolism. The TC deficiency is a rare autosomal recessive form of defective transport due to intracellular cobalamin depletion. Patients with TC deficiency present with failure to thrive and megaloblastic anemia in the early infancy period.[5-7]

In Trakadis et al[7] report, they presented 30 patients with TC deficiency from 21 unrelated families. Genetic analysis was studied in 20 of 21 unrelated families and 17 different mutations determined in the *TCN2* gene. The most prevalent symptoms at presentation in the cohort were anemia, diarrhea, and failure to thrive. They reported that the symptoms generally occurred a few weeks after birth, and became evident at 2-3 months. Nine patients who were diagnosed early due to a family history of TC deficiency, had an undelayed treatment and satisfying results were obtained. The most common morbidities were speech and attention deficits in patients under treatment. The report emphasizes that early diagnosis prevents morbid and mortal complications of the disease.[7]

Nineteen patients (17 unrelated and 2 siblings) with TC deficiency who were published in literature from Turkey summarized in Table 1.[4, 8-10] The time of diagnosis was ranged from 28 days to 7 months and the dominant clinical presentations were failure to thrive, pallor, and poor feeding in these patients. The consanguineous marriage history was identified in 8 of 12 patients. At least 1 cytopenia, mostly thrombocytopenia, was found as a hematologic finding in patients. Genetic analysis was performed in 17 patients and the most widespread mutation was homozygous c.1106+1516-1222+1231del. The common treatment regimen is weekly high-dose cobalamin (1000 mg) in these articles.[4,8-10]

Our case was diagnosed with TC deficiency based on the detection of pancytopenia while suffering from bronchopneumonia. Her history, physical examination, laboratory findings, and rapid response to treatment dragged us to diagnosis. Molecular testing resulted in a novel pathogenic homozygous c.22_31del mutation in the *TCN2* gene. Our patient did not differ in diagnosis time, clinical presentations, and treatment response from patients with different mutations published.

Cobalamin deficiency as a cause of pancytopenia in the infancy period frequently relates to cobalamin insufficiency in breast milk. A minority of patients had a hereditary inborn

Table 1. Reported Transcobalamin II Deficiencies from Turkey in the Literature

Case No	Age, Sex	Symptoms at Presentation	Consanguinity	*TCN2* Mutation	Reference Number
1	2 months, F	Failure to thrive, irritability, diarrhea	Yes	Homo. c.1106+1516-1222+1231del	4
2	28 days, M	Failure to thrive, vomiting, poor feeding	No	c.1107-347_1222+981delin 364	4
3	2 months, F	Diarrhea, vomiting, fever	Yes	Homo. c.106C>T. (Q36X)	4
4	3 months, M	Failure to thrive, poor feeding	No	Homo. c.1106+1516-1222+1231del	4
5	4 months, M	Pallor, weakness, failure to thrive	Unknown	Homo. c.1106+1516_1222 +1231del	4
6	3 months, F	Pallor, weakness, dyspnea	Unknown	Homo. c.1106+1516_1222 +1231del	8
7	2 months, F	Pallor, fever, vomiting	Unknown	Homo. c.1106+1516_1222 +1231del	8
8	2.5 months, F	Pallor, poor feeding, petechial rashes	Unknown	Homo. c.1106+1516_1222 +1231del	8
9	3 months, M	Pallor, weakness, irritability	Unknown	Not determined	8
10	2 months, M	Pallor, failure to thrive, poor feeding	Unknown	Not determined	8
11	2 months, F	Vomiting	Unknown	Homo. c.1106+1516_1222 +1231del	8
12	2 months, M	Fever, cough, diarrhea	Yes	c.940+283_286delTGGA;c.940+303_1106+764del2152insCTGG	9
13	6 months, F	Vomiting, diarrhea, failure to thrive	No	Homo. c.1106+1516_1222 +1231del	9
14	7 months, M	Poor feeding, diarrhea, petechiae	Yes	Homo. c.1106+1516_1222 +1231del	9
15	5 months, F	Vomiting, diarrhea, failure to thrive	Yes	Homo. del. of *TCN2* gene in exon 8	9
16	1 months, M	Fever, irritability, poor feeding	Yes	Homo. del. of *TCN2* gene in exon 8	9
17	2 months, M	Irritability, oral aphthous ulcers, fever	No	Homo. c.106C>T. (Q36X)	9
18	4 months, F	Fever, dyspnea, vomiting	Yes	Homo. c.241C>T (p.Gln81Ter)	10
19	4 months, M	Vomiting, diarrhea, failure to thrive	Yes	Homo. c.241C>T (p.Gln81Ter)	10
Our case	2 months, F	Dyspnea, failure to thrive, fever	No	Homo. c22_31 del.	-

M, female; F, female.

error of cobalamin metabolism. The frequency of TC deficiency as an inborn error of cobalamin metabolism increases in populations where the consanguineous marriage is common. Newborn screening for TC deficiency should be considered in these populations to prevent morbidity and mortality of the disease.

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