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A Rare Metabolic Disorder: TC II Deficiency

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Abstract

Transcobalamin (TC) deficiency is a rare autosomal recessive disease that normally manifests as megaloblastic anemia in early infancy and, in some cases, immunological deficiency, gastrointestinal and neurological symptoms. TC II deficiency has been reported in approximately 50 patients in the literator. The most appropriate treatment method for the prognosis of the disease is still unclear. In this article, we reported our patient who presented with respiratory tract infection, pancytopenia and hypogammaglobulinemia at the age of 2 months and was diagnosed with TC II deficiency. Congenital defect of cobalamin metabolism should be kept in mind in babies presenting with pancytopenia. The clinical and laboratory findings of our patient, who we have been following for about 2 years, showed that early diagnosis and appropriate treatment of this rare disease are critical for the positive course of the disease.

Keywords: Transcobalamin, Pancitopenia, Hydroxycobalamin, Hypogammaglobulinemia, Vitamins.

INTRODUCTION

Vitamin B-12 (cobalamin) is necessary for DNA synthesis and for fatty acid metabolism [1]. TC deficiency is an uncommon autosomal recessive disorder that normally manifests in early infancy, as megaloblastic anemia, and in some cases immunological deficiency and neurological symptoms [2]. The most common laboratory findings are pancytopenia, methylmalonic aciduria and homocystinuria [3]. The gene encoding for TC named as TCN2 [4]. Treatment with parenteral vitamin B12 is highly effective on clinical and biological symptoms. Significant delay in diagnosis and treatment, may result in irreversible neurological abnormalities [5]. There are 53 cases of TC deficiency reported so far in the literatüre [6]. Herein, we report TC 2 deficiency diagnosed in an infant who presented with recurrent respiratory infection, pancytopenia and hypogamaglobulinemia. We aimed to share the treatment and prognosis of this rare disease with the current literature.

CASE REPORT

A 23-month-old male patient was referred to our hospital first at the age of 2 months due to failure of response to empirical antibiotic (ceftriaxone, clarithromycin) treatment initiated in an another center for lower respiratory tract infection, the need for respiratory support and the development of cytopenia. According to the percentil curves of the Turkish children, development of his weight was 15% and height was 70%. He had bilateral rales and rhonchi in lungs. Other system examinations were normal. He was born by cesarean section on 37th week after a 6-year frozen embryo transfer. There was a 1-week history of hospitalization in the neonatal intensive care unit for pneumonia at 1 month of age. His mother and father were cousins. The patient's twin brother was a 6-year-old male who had no health problems. Neutrophils were low with 200/uL, lymphocytes were 2200/uL and platelets were 9000/uL on his hemogram. Anisocytosis, poikylocytosis,

schistocytes, microspherocytes were present, and platelets were rare and single in the patient's peripheral smear. Bone marrow aspiration revealed decreased bone marrow cellularity, myeloid predominance and decreased erythroid series. No megakaryocytes were observed. Megaloblastoid changes, dysplastic cells were seen. Hypogranulation and relative increase in promyelocytes, giant metamyelocytes and band cells were observed. The patient's plasma B12 vitamin and folic acid levels were normal with 455 pg / ml and 22.65 ng/mL. Homocysteine plasma level was high with >50.00 umol / L. According to serum immunoglobülin (IG) levels of healthy Turkish children, he had low levels of IgE, IgA, IgG. CD19 B Lymphocyte count in the patient's lymphocyte panel was low at 198 / uL (9%). The patient was given platelet suspension, intravenous immunoglobulin (IVIg) and granulocyte colony stimulating factor (G-CSF). Cyanocobalamin (CN-Cbl) treatment was administered every day for the first week, every other day for the next week, and then 100 mcg intramuscularly 2 days a week with folic asid replacement. In the follow-up, cytopenia improved and G-CSF treatment was discontinued. Cytopenia developed at the first month control of vitamin B12 treatment. A deletion of the 8th exon was detected in the TCN2 gene of the patient who was evaluated by our clinic with the preliminary diagnosis of TC II deficiency. The patient was diagnosed with TC II deficiency and started on 1000 mcg hydroxycobalamine (OH-Cbl) every day for the first week, every other day for the next week, and then once a week instead of CN-Cbl. At one month follow-up, vitamin B12 was > 1500 pg / ml and homocysteine (plasma) was normal at 5.71 umol / l. There was no cytopenia in his blood count. The patient had no active complaints at the 10-month follow-up visit. IgE, IgG was low, IgA, IgM were within normal range. Vaccine antibody response was sufficient. Laboratory findings are summarized in table 1 and table 2. In addition, the patient's neuromotor development was normal. OH-Cbl treatment was continued with 1000 mcg every 10 days. At the 23 month follow-up visit only the IgG was low and he had no active complaint.

Table 1: Laboratory Findings Of Patients Before And After Cyanocobalamin Or Hydroxycobalamin Treatment

TREATMENT	**Before treatment**	**2nd Week of CN-Cbl**	**1st Month of CN-Cbl**	**1st Month of OH-Cbl**	**OH-Cbl**	**OH-Cbl**	**OH-Cbl**
PATIENT AGE (MONTH)	2	3	4	6	10	13	20
WBC 10*3/uL,	2.9	15.4	5.1	7.3	9.5	8.3	6.9
ANC 10*3/uL,	0.2	7.2	0.2	1.4	3.1	2.4	1.6
ALC 10*3/uL,	2.2	5.9	4.5	5.1	5.6	3.2	4.4
HB g/dL,	10	12.9	8.9	12.2	11.6	12.2	12
HCT %,	29.6	38.1	26	36	35.7	36	34.6
MCV fL,	87.5	87.2	87.2	81.6	78	85	76.7
PLT 10*3/uL	9	916	118	442	448	163	251
B12 VITAMIN LEVEL (PLASMA) (N: 125-505 PG/ML)	455	979	721	>1500	>1500	1515	8530
HOMOCYSTEİNE (PLASMA) (N:5-15 umol/L)	>50.00	20.4	18	5.71	4.70	5.22	6.7

ALC: absolute lymphocyte count, ANC: absolute neutrophil count, CN-Cbl: Cyanocobalamin, HB: hemoglobulin, HCT: hematocrite, MCV: mean corpuscular volüme, N: Normal, NK: natural killer cells, OH-Cbl: hydroxycobalamin, PLT: platelets, RBC: red blood cell, WBC: white blood cell.

Table 2: Immunological laboratory findings of patients before and after Cyanocobalamin Or Hydroxycobalamin Treatment

TREATMENT	Before treatment	1st month of CN-Cbl	OH-Cbl	OH-Cbl	OH-Cbl
PATIENT AGE (MONTH)	**2**	**4**	**10**	**13**	**20**
IgG (mg/dl) (NORMAL)	259.4 (376-685)	375 (294-1165)	249.7 (463-1006)	267 (605-1430)	483 (605-1430)
IgM (mg/dl) (NORMAL)	43.1 (36-77)	36.2 (33-154)	81 (46-159)	75 (66-228)	123 (66-228)
IgA (mg/dl) (NORMAL)	<10 (9-30)	<10 (9-110)	34.4 (17-69)	38,2 (30-107)	44 (30-107)
Total IgE IU/m	<1.00	<1.00	5.55	18.4	41
PERIPHERAL LYMPHOCYTE SUB-GROUPS (NORMAL%)					
CD3+	91,0 % (48-75 %)		79 % (54-76 %)		79 % (39-73 %)
CD3+CD4+	67.9 % (33-58 %)		60.5 % (31-54 %)		52.3 % (25-50 %)
CD3+CD8+	22.6 % (11-25 %)		16 % (12-28 %)		24.5 % (11-32 %)
CD19+	9 % (14-39 %)		18 % (15-39 %)		14.6 % (17-41 %)
CD 16+56+	0.7 % (2-14 %)		3.5 % (3-17 %)		6 % (3-16 %)
CD3/HLA DR	0.5 % (1-9 %)		7.5 % (2-8 %)		4.5 % (3-12 %)

CN-Cbl: Cyanocobalamin, Ig: immunoglobulin, OH-Cbl: hydroxycobalamin.

DİSCUSSİON

Transcobalamin II (TC) deficiency is an unusual autosomal recessive disease caused by mutations in the TCN2 gene [2, 7]. Reports have described the phenotype of patients with TC deficiency with the inclusion of hematological manifestations, failure to thrive, gastrointestinal symptoms and neurological dysfunction [3]. In addition, recurrent infections can be seen in TC deficiency due to immunological abnormalities [8]. Compatible with literature pancytopenia, hypogammaglobulinemia were available in our patient. The patient's growth and development was normal and there were no digestive symptoms.

The diagnosis may be confirmed by measurement of the metabolic markers of B12 deficiency, homocysteine, and methylmalonic acid although they rarely can be within normal limits, and eventually confirmed by analyzing TC protein level and clarifying the genetic background for a TC deficiency [8, 9]. Our case had higher plasma homocysteine values although level of vitamin b12 and folic acid were normal and homozygous mutation of TCN2 gene was detected in all exon 8.

TC deficient patients have been treated with various types and practices of cobalamin. Treatment is suggested as hydroxocobalamin or cyanocobalamin with high doses of 1000 µg in order to obtain serum cobalamin levels of 1000-10.000 pg/mL, so that cobalamin can be transferred into the cell in the absence of transcobalamin in such high serum levels [10]. In most cases, better outcomes have been reported with OH-Cbl [8]. We preferred OH-Cbl treatment in our patient. During approximately 2 years of clinical follow-up, our patient's blood count and immunological parameters improved except for slight IgG decrease. Neuromotor development was consistent with age. We believe that our patient will be protected in terms of possible neurological disorders with early diagnosis and treatment with OH-Cbl treatment.

TC II deficiency; should be considered in the differential diagnosis of infants with cytopenia, neurological disorders and immunological abnormalities. Early diagnosis of this rare disease and initiation of appropriate treatment is critical for a favorable prognosis of the disease. Serum cobalamin levels of these patients should be kept particularly high (1000-10,000 pg / ml).

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