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# Early recognition and treatment of TC II deficiency: Case Report

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***Abstract*---** Transcobalamin (TC) is a carrier protein that delivers vitamin B12 to the cells. Transcobalamin II (TC II) deficiency is a very rare disease and is life-threatening if left untreated. It is an autosomal recessive disorder and needs lifelong treatment. The clinical presentation is variable, started at early infancy, and sometimes mimic severe combined immunodeficiency or acute leukemia. It includes failure to thrive, diarrhea, anemia, pancytopenia, hypotonia, developmental delay, and recurrent infection. Diagnosis of TC II deficiency is suspected based on clinical presentations with megaloblastic anemia, the elevation of plasma homocysteine, and urine methylmalonic acid level with a normal vitamin B12 and folate level. Molecular analysis of the TCN 2 gene is needed for confirmation of the diagnosis. we present a case of 2 years old Saudi boy who was admitted to the hospital with a history of fever, recurrent chest infection, failure to thrive with diarrhea, and hypotonia, and his complete blood counts showed Pancytopenia, normal vitamin B12 level and folate level, homocysteine, and urine methylmalonic acid lever were elevated. Peripheral smear and bone marrow

aspiration and biopsy revealed Hypersegmented neutrophils and megaloblastic change. We treated him with a high dose of vitamin B12 every other day with folic acid daily. Whole exome sequencing was sent and revealed Homozygous Mutation of TCN2, therefore, the diagnosis of TC II deficiency was established. The patient is now under follow-up with a once-a-week intramuscular injection of vitamin B12 with daily folic acid. In any infant with failure to thrive, recurrent infection, diarrhea and anemia, and or pancytopenia, the diagnosis of inborn error of cobalamin metabolism should be taken into consideration. Early diagnosis and aggressive treatment are extremely important for better clinical outcomes.

***Keywords*---**transcobalamin II, vitamin B12, homocysteine, TCN 2 gene.

## Introduction

Vitamin B12 and folate (vitamin B9) play an essential role in the cellular metabolism and DNA synthesis of proliferating hematopoietic stem cells (**Watkins and Rosenblatt, 2020)**. Transcobalamin (TC) is a plasma protein that facilitates the cellular uptake of vitamin B12 from blood. The first case of hereditary Transcobalamin II (TC II) deficiency was discovered in two siblings in 1971 (**Arrabal MC, 1988**) and to date, around 50 cases with TC II deficiency were diagnosed in different countries **(Engin Kose, 2020).**

TC II deficiency is an autosomal recessive disorder, caused by mutations in the *TCN2* gene, and usually presents in the first few months of life with failure to thrive (FTT), hypotonia, lethargy, diarrhea, pallor, anemia, pancytopenia, and agammaglobulinemia **(Trakadis et al,2013).** The diagnosis of TC II deficiency is usually suspected based on anemia and or pancytopenia, the elevation of homocysteine and methylmalonic acid while maintaining normal vitamin B12 and folate levels **(Trakadis et al, 2013**). Treatment with a high dose of intramuscular injection of vitamin B12 (1000mcg) is effective in restoring clinical and biological manifestations if initiated early **(Trakadis et al, 2013**) **(Arlet, 2002).** Deferred treatment can lead to serious neurological deteriorations including developmental delay, neuropathy, hypotonia, and retinal derangement (**Arlet, 2002).** Early intervention is associated with excellent outcomes.

## Case presentation

This is a case of 2 years old boy who presented at age of 1 year with a history of fever, chest infection, severe diarrhea, failure to thrive (FTT), and developmental delay**.** He was admitted as a case of acute leukemia. He is a product of full-term, normal delivery with no admission to nursery. He was admitted twice in the first year of his life due to recurrent infection and diarrhea. His vaccinations were up to

date. His parents are consanguineous with a positive family history of inborn error of cobalamin transport from the maternal side.

**Examination:** The patient did not look dysmorphic, height and weight were below 3rd centile**,** Neurological Exam: generalized hypotonia, decrease power, and normal reflexes were preserved. Chest, CVS, and Abdomen examination: Unremarkable

**Laboratory evaluations: CBC** showed (WBC 1, 5, Hemoglobin: 6, Platelet: 19, MCV: 104, ANC: 0.12 and Lymphocyte: 2.3. Peripheral smear: Hypersegmented Neutrophils **(Figure 1)**. With normal serum B12 and folate levels. Liver, renal, and bone profile panels were normal. High serum homocysteine (22 mcg/l, normally 5-15 mcg/l), and urine methylmalonic acid levels (5.6mmol/mol CRT, normally <3.6mol/mol CRT).

**Hb electrophoresis**: HbF: 6% (normally less than 1%).

**Bone marrow aspiration and biopsy revealed**: normoblast with megaloblastic changes (Figure 2) and dyserythropoietic (Figure 3)**.**

Based on his clinical scenario, laboratory investigations, and family history, a high dose of Vitamin B12 with 1000mcg every other day and 1mg of folic acid daily were initiated.

After ten days, the patient's symptoms improved significantly and his complete blood counts were back to normal **(Table1)**

As a result, the patient was discharged home and 1000mcg IM of vitamin B12 once a week with folic acid was prescribed. At the time of writing this report,

The patient is in good general health condition, developmentally normal, height and weight reached the 25th centile with normal complete blood counts.

Whole exome sequencing was sent during inpatient care and the result obtained after two months revealed a **Homozygous Mutation of TCN2** hence the diagnosis of TC II deficiency was made.

Table 1
Shows complete blood counts with differential (CBCD) pretreatment, after treatment during hospitalization, and upon his follow up

| | Before treatment | | | | after treatment | | | On follow up | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Date | 1/7 | 2/7 | 3/7 | 4/7 | 6/7 | 8/7 | 12/7 | 27/9 | 1/11 | 4/2 |
| WBC | 1.6 | 1.4 | 1.2 | 2 | 5 | 11 | 18 | 11.3 | 9 | 7.5 |
| Hb | 5.2 | 7 | 6.7 | 7.8 | 8.9 | 9.5 | 9 | 11.2 | 12 | 12.2 |
| MCV | 104 | 102 | 101 | 99 | 94 | 89 | 90 | 88 | 90 | 85 |
| Platelet | 19 | 52 | 40 | 21 | 99 | 157 | 357 | 222 | 243 | 175 |
| ANC | 0.01 | 0.02 | 0 | 0,08 | 1.5 | 4 | 5.3 | 4.2 | 2.7 | 1.6 |

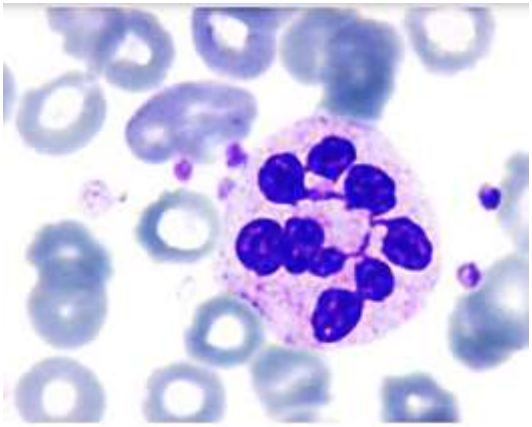

Figure 1. Hypersegmented neutrophils

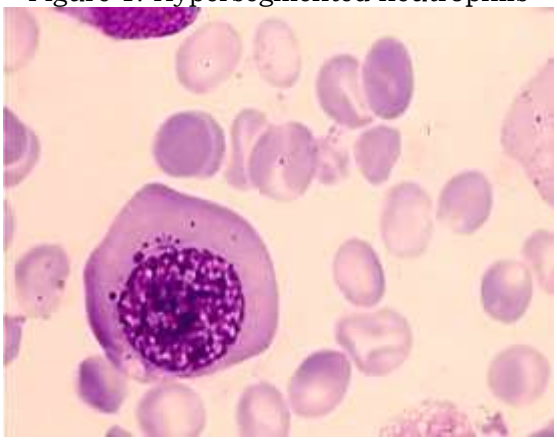

Figure 2. Megaloblastic changes

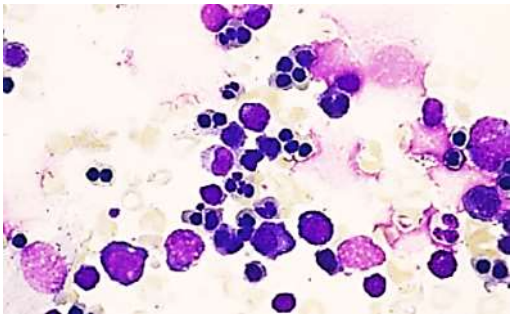

Figure 3. Dyserythropiesis

**Discussion**

Transcobalamin (TC) is a carrier protein and it drives cobalamin into cells. **C.M. Pfeiffer (2013),** reported that Vitamin $B_{12}$ status can be assessed by measuring serum or plasma cobalamins and serum holo-transcobalamin II (holo TC II). Consistent with a previous finding **(Selma Unal, Feryal Karahan,2018),** serum vitamin B12 level is always normal in cases of TC II deficiency due to the short duration of plasma half-life of holo TC II which lasts for five minutes resulting in serum vitamin B12 in the serum is bound to TC-I and III. In the presented case, the elevation in serum homocysteine and urine methylmalonic acid levels and low level of IgG has been reported in another study (**Robert, M. Kliegman,** 2020's work).

The most reported cases of TC II deficiency have the same clinical presentation which sometimes resembled acute leukemia or severe combined immunodeficiency, (87.5% of patients have hematological abnormalities including anemia and or pancytopenia, 66.6% had FTT, 37.5% had gastrointestinal findings and neurological impairment in 29% of cases) (**Trakadis et al, 2013)**. The clinical symptoms occur as early as the age of 3–5 weeks and the neurological symptoms appear 3–6 months after the onset of symptoms (**Philip Lanzkowsky, 2016)**

In our patient, the primary diagnosis was acute leukemia because the initial CBC found that the patient had severe pancytopenia. During hospitalization, the patient was transfusion dependent with packed red blood cells and platelet and he required antibiotics due to febrile neutropenia. After initiating treatment of vitamin B12 and folic acid, CBC counts returned to normal, and significant improvement in symptoms was observed. This suggests that early treatment can lead to improved clinical symptoms and prevent serious complications (**Kaikov Y, Wadsworth L, Hall C, and Rogers P.).**

The gene responsible for TC II deficiency TCN 2 is located on chromosome 22. In a previous cohort study for 30 patients with TC II deficiency**(Trakadis et al, 2013)** Molecular analyses were done for 20 of them, 16 had a homozygous mutation of TCN 2, and the remaining cases were found to have the compound heterozygous mutation. Most reported mutations were deletions in TCN 2 gene, like our presented case, or insertions. Point mutations and nonsense mutations also had been reported in the literature **(Watkins and Rosenblatt 2011a; Li et al 1994a**.), (**Li et al 1994b; Namour et al 2003).**

The overall clinical and laboratory improvement noticed in our patient after early treatment with IM injection of vitamin B12 and folic acid aligns with what had been reported in previous work **(Trakadis et al, 2013).** Out of the 30 reported cases, nine cases received treatment in the neonatal period and have had optimal outcomes. One out of the nine cases was diagnosed during the neonatal period by newborn metabolic screening which suggests the utility of using newborn screening (NBS) to detect TC II deficiency?

Lifelong treatment with vitamin B12 at least once a week is important to prevent disease relapse as it has been documented that two cases relapsed after discontinuing the treatment **(Trakadis et al, 2013). , (Yeldrim ZK, 2014), (Manual S, 2019).** Speech deficits, attention deficit, tremors, and visual disturbance were the most common complications for patients on long treatment with IM injection as reported **(Trakadis et al, 2013)** however, none of these complications have been developed in our patient. Our study supports that early disease detection and initiation of adequate treatment are critical to disease control and ensuring a better outcome.

## Conclusion

TC II deficiency is a very rare disease and is life-threatening if left untreated. The diagnosis of TC II deficiency should be considered for any infant with failure to thrive, anemia, recurrent infection, and developmental delay. Early detection of TC II deficiency and aggressive treatment are associated with optimal disease outcomes. A newborn metabolic screening might be helpful in the detection of TC II deficiency. The families of affected children should receive proper genetic counseling.

**List of abbreviations**

- IgG: immunoglobulin
- Hx: history
- WBC: white blood cells
- Hb: Hemoglobin
- MCV: mean corpuscular volume
- ANC: absolute neutrophilic counts
- (TC): Transcobalamin
- (holo TC): Holotranscobalamin
- (FTT): failure to thrive
- (NBS): newborn screening

**Conflict of Interest**
None

**Funding**
None

**Consent for publication**

Informed consent was taken from the patient to publish this case report in a medical journal

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