Early recognition and treatment of TC II deficiency: Case Report

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Abstract---Transcobalamin (TC) is a carrier protein and it delivers vitamin B12 to the cellular TC receptor. TC II deficiency is a very rare disease and is life-threatening if left untreated. It is an Autosomal recessive disease and needs lifelong treatment. The clinical presentations are variable, started at early infancy, and sometimes mimic severe combined immunodeficiency or acute leukemia. It includes failure to thrive, diarrhea, anemia and or 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 level of vitamin B12 and folate. 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. Though, normal vitamin B12 level and folate level, homocysteine, and urine methylmalonic acid level were elevated. Peripheral smear and bone marrow aspiration and biopsy revealed Hypersegmented neutrophils and megaloblastic change. We treated him empirically with a high dose of vitamin B12 every other day which showed clinical and laboratory improvement. 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 who presented with failure to thrive, recurrent

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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 cells such as hematopoietic stem cells. (Watkins and Rosenblatt, 2020). Vitamin B12 is an animal origin and it is synthesized by bacteria in the gut acquired sources are limited to meat, fish, milk, eggs, certain algae, and bacteria. TC is a plasma protein that facilitates the cellular uptake of vitamin B12 from blood. The first case reported of hereditary TCII deficiency in two siblings was in 1971 (Arrabal MC,) and to date, around 50 cases with TC deficiency were diagnosed in different countries (ngin Kose). It is an autosomal recessive disorder that presents in the first months of life with failure to thrive, hypotonia, lethargy, diarrhea, pallor, anemia, pancytopenia, and agammaglobulinemia caused by mutations in the TCN2 gene and usually (Trakadis et al). The diagnosis of TC deficiency is suspected based on anemia and or pancytopenia, and the elevation of homocysteine and methylmalonic acid, although, vitamin B12 and folate levels are normal (Trakadis). Treatment with a high dose of intramuscular injection of vitamin B12 is effective in restoring clinical and biological manifestations if initiated early (Trakadis) (Arlet,). Deferred treatment can all lead to serious neurological deteriorations including developmental delay, neuropathy, hypotonia, and retinal derangement (Arlet,). Early intervention is associated with excellent outcomes.

**Case presentation**

This is a case of 2 years old boy, who was 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 highly suspicious acute leukemia. He is a product of full-term, NSVD with no admission to NICU. He required admission twice in the first year of life due to recurrent infection and diarrhea. Upon reviewing the Hx, his vaccinations are up to date, parents are consanguineous with a positive family history of inborn error of cobalamin transport from the maternal side.

**Examinations**

The patient did not look dysmorphic, height and weight were below 3centile, Neurological Exam: generalized hypotonia, decrease power, and normal reflexes were preserved.

- Chest: decrease air entry with crepitation
- 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 S.B12 and folate levels. Hb electrophoresis: HbF: 6% (normally less than 1%). Bone marrow aspiration and biopsy revealed: Monocellular with normoblast with megaloblastic changes (Figure 2) and dyserythropiesis (Figure 3). Normal liver, renal, and bone profile panel. Elevated serum homocysteine (22 mcg/l) and urine methylmalonic acid level. Based on his clinical scenario, laboratory investigations, and family history, he was started empirically on a high dose of Vitamin B12 with 1000mcg every other day with 1mg of folic acid daily. After seven days, his fever subsided, and his diarrhea resolved with normalization of complete blood count. (Table 1). So, we discharged him home in good general condition and to continue on 1000mcg IM of vitamin B12 once a week with folic acid. Now, he is alive, he is 2 years old, developmentally normal, height and weight were significantly improved, and reached the 25th centile with a normal complete blood count. Whole exome sequencing was sent and came after two months as a Homozygous Mutation of TCN2 and 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

<table>
<thead>
<tr>
<th>Date</th>
<th>Before treatment</th>
<th>after treatment</th>
<th>On follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/7</td>
<td>2/7</td>
<td>3/7</td>
</tr>
<tr>
<td>WBC</td>
<td>1.6</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Hb</td>
<td>5.2</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>MCV</td>
<td>104</td>
<td>102</td>
<td>101</td>
</tr>
<tr>
<td>Platelet</td>
<td>19</td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td>ANC</td>
<td>0.01</td>
<td>0.02</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Hypersegmented neutrophils
Discussion

Transcobalamin (TC) is a carrier protein that drives cobalamin from the blood into cells. (C.M. Pfeiffer, 2013) reported that Vitamin B<sub>12</sub> status can be assessed by measuring serum or plasma cobalamins and serum holo-transcobalamin II. Normal S.B12 and folate levels in constricted with Selma3 found that serum vitamin B12 levels have been reported to be normal in cases of TC deficiency. Since the plasma half-life of holo TC-II is approximately a minute and all measured serum vitamin B12 in the serum is bound to TC-I and III. So, patients with TC-II deficiency typically have a normal level of serum vitamin B12. In the presented case, elevation in serum homocysteine and urine methylmalonic acid level and low level of IgG is consistent with Robert 4M. Kliegman 2020’s work. The clinical features of TC II deficiency have been similar in most of the reported cases and sometimes mimic acute leukemia or severe combined immunodeficiency (SCID). Trakardis et.al 5 reported that 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.

Another study by Philip Lanzkowsky, 2016 reported that patients with TC-II deficiency present clinically at age of 3–5 weeks symptoms and neurological symptoms appear 3–6 months after the onset of symptoms. In our patient, the primary diagnosis was acute leukemia because his initial CBC found that he had severe pancytopenia.
During his hospitalization, he was transfusion dependent with packed red blood cells and platelet and he required antibiotics due to febrile neutropenia after empirical treatment with vitamin B12, his CBC counts showed complete recovery, and a clear improvement in his symptoms was observed and this suggests that early case finding and early treatment will improve the clinical situation and prevent serious complications. (Kaikov Y, Wadsworth L, Hall C, Rogers P.).

The gene for TC-II deficiency TCN 2 is located on chromosome 22. A previous cohort study for 30 patients with TC-II deficiency was done by (Trakadis et al). Molecular tests were done for 20 of them, 16 patients had a homozygous mutation of TCN 2 and the remaining cases were compound heterozygous mutation. Most reported mutations were deletions in TCN 2 gene like our presented case or insertions (Watkins and Rosenblatt 2011a; Li et al 1994a.). Point mutations and Nonsense mutations also had been reported (Li et al 1994b; Namour et al 2003). The clinical improvement of our presented case after early empirical treatment with IM injection of vitamin B12 in the same line aligns with previous work done by Y. J. (Trakadis et al) that states early diagnosis and treatment will reverse the clinical condition soon. Also, Trakardis et al reported nine cases were received treatment in the neonatal period and have had optimal outcomes. One out of nine cases was diagnosed by newborn metabolic screening so, can we use newborn screening (NBS) to detect TC deficiency? Lifelong treatment with vitamin B12 at least once a week is the mainstay to prevent disease relapse (Trakadis et al, Yeldirim ZK and Manual S). Speech deficits, attention deficit, tremors, and visual disturbance were the most common complications for patients on chronic treatment with IM injection as per reported by (Trakadis et al) but none of them were developed in our case. Our study supports that early detection of the disease and initiation of adequate treatment is critical for control of the disease and ensuring a better outcome.

**Conclusion**

TC-II deficiency is a very rare disease and life-threatening if left untreated. The diagnosis of TC II deficiency should be kept in mind for any child with failure to thrive, anemia, recurrent infection, and developmental delay. Early detection of TC II deficiency and aggressive treatment is associated with good disease control and better clinical outcome. The families of affected children should receive proper genetic counseling. A newborn screen might be helpful in the detection of TC deficiency.

**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
• (NSVD): normal spontaneous vaginal delivery
• (NICU): nursery intensive care unit

Conflict of Interest
None

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

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