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Transcobalamin II Deficiency Can Present without Hematological Manifestations: A Novel TCN2 Gene Variant

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Transcobalamin II (TC) deficiency is a rare but serious metabolic disorder. It usually presents in the first year of life with failure to thrive, megaloblastic anemia and pancytopenia. Other features includes hypotonia, ataxia, lethargy, vomiting, diarrhea, mucosal ulceration, recurrent infections, agammaglobulinemia, methylmalonic aciduria and in rare cases, seizures. Besides, clinical presentation of TC deficiency may not be obvious thus leading to complex issues around diagnosis and treatment. Herein, we present TC II deficiency diagnosed in a 14 months old boy who presented with progressive myoclonic seizure, ataxia, truncal hypotonia, without any hematological manifestations and found to have a novel variant in the TCN2 gene.

Keywords: Transcobalamin II deficiency; TCN2 gene; megaloblastic anemia; pancytopenia; neurological deficits.

1. INTRODUCTION

"Cobalamin (vitamin B12, Cbl) plays an important role in the metabolism and DNA synthesis of proliferating cells" [1]. "Generally, if any infant presents with pancytopenia and normal vitamin B12 and folate levels, inherited disorders of cobalamin or folate metabolism should be

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consider. However, clinical presentation of transcobalamin deficiency may not be obvious thus leading to complex issues around diagnosis and treatment" [1-2].

"Transcobalamin II (TC) is an essential plasma protein for the absorption, transportation, and cellular uptake of cobalamin. Transcobalamin deficiency is a rare autosomal recessive disorder initially described in 1971" [3]. "It is caused by mutations in the TCN2 gene and usually presents in infancy with failure to thrive, megaloblastic anemia and pancytopenia. Other features includes hypotonia, lethargy, vomiting, diarrhea, mucosal ulceration, recurrent infections, agammaglobulinemia and methylmalonic aciduria. Besides, although rarely, the disease may resemble severe combined immunodeficiency disease (SCID) and hematological malignancy" [1-6].

"The diagnosis of TC deficiency is suspected based on megaloblastic anemia and accumulation of homocysteine and methylmalonic acid, whereas vitamin B12 and folate levels are normal" [2,5-7]. "Treatment with parenteral cobalamin is highly effective in improvement of clinical and biological manifestations TC deficiency. Periodic cobalamin supplementation if started early likely reverse the clinical manifestations" [5,8]. "Delayed or inadequate treatment may result in neurological abnormalities, including developmental delay, neuropathy, myelopathy, and retinal degeneration" [2, 4,5,9,10]. "To date, 27 pathogenic mutations in TCN2 gene have been identified and almost 62 patients with TC deficiency have been reported from different countries and ethnic groups" [6].

Herein, we present a case of TC deficiency in our patient, who presented with isolated progressive myoclonic seizure, ataxia, truncal hypotonia, without any hematological manifestations and found to have a novel variant in the TCN2 gene.

2. CASE REPORT

A 14-month-old boy was born at full term after an uneventful pregnancy of 38 weeks. His birth weight was 3 Kg and his head circumference was 33.7 cm. No history of polyhydramnios, reduced fetal movement, no evidence of in utero seizures, and no immediate postnatal complications. His initial complete blood count was unremarkable (Hb: 13 g/L, MCV 96 fL). Expanded newborn screening, including tandem mass spectrometry, detected no abnormalities.

At 9 months of age, he was presented with developmental regression. He was initially developing normally until four months of age, after which the parents noted a gradual loss of motor and speech skills. At the age of 11 months, he manifested unsteadiness and shaking hands when reaching objects. He also had recurrent episodes of head nodding, then he developed myoclonus mostly in the upper extremities, which progressed, as well as abnormal rhythmic eye movements. Overall, the clinical manifestations were progressive, negatively affecting the child and parents.

In the past, the parents noted two episodes of febrile seizures and the onset of neuroregression that followed a second febrile seizure as well as repeated chest infections. He has an up-to-date vaccination history. The family history was significant with generalized childhood/ adolescent-onset epilepsies with unknown etiology. A sister of his died at age 7 of unexplained hepatic failure, and he was the fourth child of first-degree cousins. The older brother was diagnosed with anemia of unknown etiology.

Clinical examination at 12 months of age showed that the head circumference was normal. He was not cyanosed or pale, and had no neurocutaneous markers. He was irritable, neurologically had poor visual attention, nystagmoid eye movement, excessive startle response, prominent tongue fasciculations, clinical evidence of bulbar dysfunction, myoclonus involving upper extremities, generalized hypotonia, hyporeflexia, truncal unsteadiness, and polyminimyoclonus. The dilated fundal examination revealed no specific findings in the optic disc, no pallor, no retinal degeneration, and no cherry-red spots, along with mild hepatomegaly of 2 cm.

His complete blood count repeated many times was essentially normal, however at the age of 10 months MCV started to increase, the other indices were unchanged. His liver function tests revealed slightly raised transaminases, normal coagulation, albumin and bilirubin levels. Renal profile and electrolytes were normal. Ammonia and lactate were also within normal levels. Brain MRI, at 9 months of age was normal, and repeated one at the age of 14 months revealed cerebral atrophy and poor myelination. In

interictal electroencephalography, ploy pikes and slow wave run of 4 to 6 Hz were repeatedly observed. Photosensitivity was also positive. A whole exome sequencing result revealed a homozygous mutation at the acceptor site of intron 4 of TCN2 gene, c.3 G > A- P(Met1), chr 22: 31003321, NM_000355.4.

He was initially treated with levetiracetam, clonazepam, and multivitamins, which partially alleviated the myoclonus. At 14 months of age, once the genetic test was available, treatment with 1 mg of intramuscular hydroxocobalamin daily was initiated for 1 week, then shifted to 1 mg of intramuscular hydroxocobalamin twice a week. Neurological examination were used to monitor the clinical response. These monitoring concepts were complemented by CBC and clinical neurological examination, and serial electroencephalographic as a surrogate marker for epileptic encephalopathy. The patient exhibited a response to the cobalamin therapy by becoming more energetic, exhibiting rise in hemoglobin level along with decline in MCV.

Family history revealed that his elder brother had history of sudden onset of macrocytic anemia and mild neutropenia at the age of 4 years. His cognitive functions were intact, however he showed some neurological deficit. His CBCD showed; WBC 4.4-9.2 x 10^9/L, ANC 0.52 – 1.8 10^9/L, platelets count 224-448, Hb 9.8-12.7 g/L, MCV 94.5 fL. Peripheral smear showed high number of hyper segmented neutrophils (85%). Immunoglobulins level, vitmain B 12 level (457 pg/ml) and folic acid level (9.7 ng/dl) were all normal. Homocysteine level was also normal, however methymalonic acid level was high. He was also receiving intramuscular hydroxocobalamin with good response in terms of this improvement in hemoglobin level and neutropenia. We recommend that a genetic study should be conducted to find the possible genetic heterogeneity of TCII deficiency in this family as both of them had different presentations and clinical manifestations.

3. DISCUSSION

Most of previous reports identified the hematological findings i.e. macrocytic anemia or pancytopenia as the most common clinical feature of TC deficiency but absence of hematological manifestations in our case emphasize that TC deficiency can present with isolated neurological findings and can leads to delay in early diagnosis and prompt initiation of treatment which is crucial for better clinical outcome. Moreover, a novel likely pathogenic variant was described in this report. Further, this report emphasizes that early and intensive treatment is crucial for better clinical outcomes.

“In general if severe anemia mostly megaloblastic and pancytopenia present in the infancy, transcobalamin deficiency should be considered in the working differential diagnosis. In most of the previous reports, TC deficient patients present with cytopenias and anemia” [5,6,11]. “Further, the most common clinical presentation of the disease is hematological complications. Hematological findings, including anemia or pancytopenia was reported in up to 87.5% of patients” by Trakadis et al. [5]. “Although the hematological findings are consistent with macrocytic anemia, vitamin B12 levels are typically within the normal range” [3, 6]. In our case, we did not observe macrocytic anemia or pancytopenia, rather he presented with isolated neurological manifestations, which could be the reason for delay in diagnosis, the difference in the clinical manifestation may be related to types of variants and site, as well as epigenetic.

“Neurologic manifestations of B12 deficiency are polymorph” [12-13]. “Usually, neurologic and psychiatic features of B12 deficiency are rarely an initial symptoms. They are usually attributed to the intervention of vitamin B12 in the isomerization reaction of methylmalonic acid to succinic acid. Neurological involvement often occurs along with macrocytic anemia but can arise in the absence of either anemia or macrocytosis” [12-14]. “Moreover, it is not clear why vitamin B12 deficiency leads to hematological disease in some patients and neurological disease in others. The well documented major manifestations identified are peripheral neuropathy, dementia, subacute combined degeneration of spinal cord, optic atrophy, psychosis and mood disturbance” [12,13,15].

Trakadis et al. reported hematological findings, including pancytopenia, also they found in their report delayed milestones, hypotonia, dyslexia, decreased IQ, vertigo, plantar clonus and personality disorder, in contrast to our case, they didn’t report seizures [5]. In our case, we did not found significant hematological manifestations such as pancytopenia, rather he presented with isolated neurological manifestations, which could be the reason for delay in diagnosis. The

difference in the clinical manifestations may be related to types of variants and site, as well as epigenetic. They found a variant in the *TCN2* gene (c.501 503delCCA; c.1115 1116CA). These mutations affect the interaction between transcobalamin and transcobalamin receptors. In contrast, we have found a different mutation site and different mechanisms which result in a loss of the start codon, and affect the formation of a protein by an mRNA. According to Kose et al., transcobalamin 2 deficiency has been linked to several clinical signs, including severe truncal hypotonia, severe neurologically significant developmental delay, and hypogammaglobulinemia. The bone marrow was hypocellular, in terms of clinical manifestations, the unique pathogenic homozygous c.241C>T (p. Gln81Ter) in *TCN2* gene was revealed [6], the variant differs from our new mutation; this difference could be attributed to the mutation site and epigenetic factors.

"Another clinical manifestation of TC deficiency is gastrointestinal complications. A report declared that 37.5% of patients have gastrointestinal findings" [5]. "Gastrointestinal manifestations occur because of interruption of proliferation of epithelial cells of the gastrointestinal tract which causes atrophy of the epithelial cells of the luminal lining" [16]. "Patients usually present with vomiting, loose motion, failure to thrive, and rarely mucositis and glossitis" [17]. However our patient did not had any of these symptoms. Usually gastrointestinal symptoms and low immunoglobulin levels were resolved with i.m. hydroxy-Cbl treatment.

"It is well documented that prompt initiation of treatment is crucial for achieving optimal outcomes" [5, 10]. Many reports identified that early treatment has better outcomes [5,6,9,10]. "Neurological and hematological deterioration have been reported in patients who discontinued treatment, thus lifelong treatment is required for the prevention of these complications" [5,10,18]. "There is no clear consensus about the dosage, dose intervals, route of administration (i.m., oral), and the form of cobalamin for the management of TC deficiency" [6]. "However, aggressive treatment, which comprises parenteral or intramuscular high-dose (1 mg) injection (weekly at least), is highly recommended" [5, 6,10]. "Besides, compared with the cyanocobalamin treatment, better clinical results reported with hydroxycobalamin treatment" [5]. "Moreover, successful clinical outcome were also reported in two patients with 1 mg i.m. weekly methylcobalamin" [19]. "Management with folic acid and betaine were also reported in some studies" [9]. In our cases, after one week of intensive treatment, significant clinical improvements were observed. In the short follow-up period, with weekly i.m. hydroxy-Cbl treatment, neurological examination findings were normal. We believe that, more reports and prospective clinical trials will be helpful for determining the most appropriate treatment approach in TC deficiency.

"Previously, insertions, deletions, splice-site, and nonsense mutations were reported in TC deficiency, however no genotype-phenotype correlation was observed" [6]. In our patient, we identified the homozygous variant [c.3G>A p.(Met1?) chr22:31003321] this can lead to a loss of the start codon, so that an effect on the translation appears conceivable. A family study should be conducted for the genetic heterogeneity of TCII deficiency. More reports of novel variations may help to evaluate the genotype-phenotype relationship better.

4. CONCLUSION

In summary, the inborn error of cobalamin metabolism should be considered in infants with pancytopenia, growth retardation, gastrointestinal manifestations, and immunodeficiency. Although the magaloblastic anemia and pancytopenia are the most common findings, clinical presentation of TC deficiency may not be obvious thus leading to complex issues around diagnosis and treatment. Thus, a high index of suspicion should be exercise while dealing infants with unexplained neurological findings as early diagnosis and aggressive treatment of TCII deficiency with high-dose cobalamin are crucial for better clinical outcomes.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, Ueland PM, Yajnik C. Vitamin B_{12} deficiency. Nat Rev Dis Primers. 2017;3:17040.
2. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014;349: 5226.
3. Hakami N, Neiman PE, Canellos GP, Lazerson J. Neonatal megaloblastic anemia due to inherited transcobalamin II deficiency in two siblings. N Engl J Med 1971;285:1163–70.
4. Nawaz A, Khattak NN, Khan MS, Nangyal H, Sabri S, Shakir M. Deficiency of vitamin B12 and its relation with neurological disorders: A critical review. J. Basic Appl. Zool. 2020;81:1–9.
5. Trakadis YJ, Alfares A, Bodamer OA, et al. Update on transcobalamin deficiency: clinical presentation, treatment and outcome. J Inherit Metab Dis. 2014;37: 461–73.
6. Kose E, Besci O, Gudeloglu E, et al. Transcobalamin II deficiency in twins with a novel variant in the TCN2 gene: case report and review of literature. J Pediatr Endocrinol Metab. 2020;33(11):1487-1499.
7. Alam MM (editor). In book, A Practical Guide I Pediatric Hematology. Lulu Press, Morrisville (USA). 2021; p3-7.
8. Arlet JB, Varet B, Besson C. Favorable long-term outcome of a patient with transcobalamin II deficiency. Ann Intern Med. 2002;137:704–5.
9. Schiff M, Ogier de Baulny H, Bard G, Barlogis V, Hamel C, Moat SJ, et al. Should transcobalamin deficiency be treated aggressively?. J Inherit Metab Dis. 2010;33:223–9.
10. Yildirim ZK, Nexo E, Rupar T, Büyükavci M. Seven patients with transcobalamin deficiency diagnosed between 2010 and 2014: a single-center experience. J Pediatr Hematol Oncol. 2017;39:38–41.
11. Prasad C, Rosenblatt DS, Corley K, Cairney AE, Rupar CA. Transcobalamin (TC) deficiency–potential cause of bone marrow failure in childhood. J Inherit Metab Dis. 2008;31:S287–92.
12. Ammouri W, Harmouche H, Khibri H, Benkirane S, Azlarab M, et al. Neurological Manifestations of Cobalamin Deficiency. Open Access J Neurol Neurosurg. 2019; 12(2): 555834.
13. Maamar M, Tazi-Mezalek Z, Harmouche H, et al. Neurological manifestations of vitamin B12 deficiency: a retrospective study of 26 cases. Rev Med Interne. 2006;27(6):442-7.
14. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988; 318(26): 1720-1728.
15. Serin HM, Arslan EA. Neurological symptoms of vitamin B12 deficiency: analysis of pediatric patients. Acta Clin Croat. 2019;58(2):295-302.
16. Bibi H, Gelman-Kohan Z, Baumgartner ER, Rosenblatt DS. Transcobalamin II deficiency with methylmalonic aciduria in three sisters. J Inherit Metab Dis. 1999; 22:765–72.
17. Herrmann W, Obeid R. Cobalamin deficiency. Subcell Biochem. 2012;56:301–22.
18. Ünal S, Karahan F, Arıkoğlu T, Akar A, Kuyucu S. Different presentations of patients withtranscobalamin II deficiency: a singlecenter experience from Turkey. Turk J Haematol. 2019;36:37–42.
19. Nashabat M, Maegawa G, Nissen PH, et al. Long-term outcome of 4 patients with transcobalamin deficiency caused by 2 novel TCN2 mutations. J Pediatr Hematol Oncol. 2017;39:e430–6.

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