Case report

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

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 aciduriaand, in rare cases, seizures.However, 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.

Key Words: Transcobalamin II deficiency, TCN2 gene, megaloblastic anemia, pancytopenia, neurological deficits

INTRODUCTION

Cobalamin (vitamin B12, Cbl) plays an important role in the metabolism and DNA synthesis of proliferating cells [1].Generally, if pancytopenia presents in young infants with normal vitamin B12 and folate levels, inherited disorders ofcobalamin or folate

metabolism should be consider. However, clinical presentation of transcobalamindeficiency 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.TC deficiency is a rareautosomal recessive disorder initially described in 1971[3].It is caused by mutations in the TCN2gene and usually presents in the first year of lifewith 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 severecombined immunodeficiency disease and hematological malignancy [1-6].

The diagnosis of TC deficiency is suspected based onmegaloblastic anemia and accumulation of homocysteineand methylmalonic acid, whereas vitamin B12 and folatelevels are normal [2, 5-7]. Treatment with parenteral cobalaminis highly effective in improvement of clinical and biological manifestations.Clinical manifestations are reversible if periodic cobalaminsupplementation is initiated early [5,8]. Delayed or inadequatetreatment may result in neurological abnormalities,including developmental delay, neuropathy, myelopathy, and retinal degeneration [2, 4,5, 9, 10]. To date, almost 60 patientswith TC deficiency have been reported from differentcountries. Twenty-five pathogenic mutations in TCN2 genehave been identified [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.

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 gm/dl, MCV 96). Expanded newborn screening, including tandem mass spectrometry, detected no abnormalities.

Comment [RKBdS1]: g/dL

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 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.

Comment [RKBdS2]: in the past

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 inter-ictal electroencephalographyploys 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 used monitor the clinical and biochemical 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 energetic, exhibiting mouth.

Comment [RKBdS3]: interictal

Comment [RKBdS4]: Can you check this word?

Comment [RKBdS5]: This sentence does not make sense.

Comment [RKBdS6]: What does that mean?

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 findingsand can leads to delay in early diagnosis and prompt initiation of treatment which is crucial for better clinicaloutcome.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 and pancytopenia present in the infancy, TC deficiency should be considered in the differentialdiagnosis. Most of the previously reported TC deficiencypatients present with pancytopenia and anemia[5,6,11]. Moreover, the most common clinicalfeature of the disease is hematological complications.Trakadis et al. reported that 87.5% of patients havehematological findings, including anemia or pancytopenia[5]. Although the hematological findings arecompatible with macrocytic anemia, vitamin B12levels are typically within the normal range [3, 6]. In ourcase, we did not observed 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.

Comment [RKBdS7]: observe

Neurologic manifestations of B12 deficiency are polymorph[12-13]. Neurologic and psychiatic manifestations of B12 deficiency are rarely initial symptoms. They are usually attributed to the intervention of vitamin B12 in the isomerization reaction of Methylmalonic Acid (MMA) to succinic acid. Neurological involvement often occurs along with macrocytic anemia but can arise in the absence of either anemia or macrocytosis[12-14]. Also, it is unclear why vitamin B12 deficiency leads to neurological disease in some patients and hematological disease in others. The well-known major manifestations described include peripheral neuropathy, subacute combined degeneration of spinal cord, dementia, optic atrophy, psychosis and mood disturbance. Other, neurological disorders also described are cerebellar ataxia, abnormalities of

cranial nerves, Parkinsonian syndrome and movement disorders[12,13,15]. Our case presented with progressive myoclonic seizure, ataxia and truncal hypotonia.

Another clinical manifestation of TC deficiency is gastrointestinal complications. A cohort study declaredthat 37.5% of patients have gastrointestinal findings [5]. Gastrointestinal manifestations occur because of interruption of proliferation of epithelial cells of thegastrointestinal tract which causes atrophy of the epithelial cells of the luminal lining [16]. Patients usuallycomplain of vomiting, diarrhea, failure to thrive, and rarely mucositis glossitis [17]. However our patient did not had any of these symptoms. Usually gastrointestinal symptoms and low immunoglobulinlevels were resolved with i.m. hydroxy-Cbltreatment.

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 ofcobalaminfor the management of TC deficiency [6].However, aggressivetreatment, which comprises parenteral or intramuscularhigh-dose (1 mg) injection (weekly at least), is highly recommended[5, 6,10]. Besides, compared with the cyanocobalamintreatment, better clinical results reported with hydroxycobalamin treatment [5]. Moreover, successful clinical outcome were also reportedin two patients with 1 mg i.m. weekly methylcobalamin[19]. Folic acid and betaine administrations were alsoreported in TC deficiency [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 appropriatetreatment approach in TC deficiency.

No genotype-phenotype correlation was reported in TCdeficiency. Previously, insertions, deletions, splice-site,and nonsense mutations were reported [6]. Inour patient, we identified the homozygous variant [c.3G>A p.(Met1?) chr22:31003321]this can leads to a loss of the start codon, so that an effect on the translation appears conceivable.More reportsof novel variations may help to evaluate the genotype-phenotyperelationship better.

CONCLUSION

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

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