Case report

Transcobalamin deficiency: vitamin B_{12} deficiency with normal serum B_{12} levels

Sanjeev Khera,[1] Suman Kumar Pramanik,[2] Saroj Kumar Patnaik[1]

[1]Pediatrics, Army Hospital Research and Referral, New Delhi, India
[2]Hematology, Army Hospital Research and Referral, New Delhi, India

Correspondence to
Dr Sanjeev Khera;
kherakherakhera@gmail.com

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SUMMARY

Transcobalamin (TC) deficiency is a rare autosomal recessive inborn error of cobalamin transport which clinically manifests in early infancy. We describe a child with TC deficiency who presented with classical clinical and lab stigmata of inborn error of vitamin B_{12} metabolism except normal serum B_{12} levels. He was started on empirical parenteral cobalamin supplements at 2 months of age; however, the definitive diagnosis could only be established at 6 years of age when a genetic evaluation revealed homozygous nonsense variation in exon 8 of the TCN2 gene (chr22:g.31019043C>T).

BACKGROUND

Cobalamin (B_{12}) has three carrier proteins namely haptocorrin (formerly transcobalamin I) which binds majority of B_{12}, transcobalamin (TC) (formerly transcobalamin II)—which is responsible for the endocytosis of B_{12} from blood to cells and intrinsic factor which has an important role in absorption of B_{12}. TC deficiency (OMIM#275350) is an uncommon autosomal recessive inborn error of cobalamin transport which clinically manifests in infancy. It is characterised by clinical signs and symptoms of B_{12} deficiency with megaloblastic changes in bone marrow, raised plasma homocystine and high urinary/plasma methylmalonic acid (MMA) but with normal serum B_{12} levels. Diagnosis is established by TC assays in cultured fibroblast or analysis of TCN2 gene. Clinical manifestations are reversible if periodic cobalamin supplementation is initiated early.[1–3]

We present a case wherein there was a strong suspicion of inborn error of vitamin B_{12} deficiency since the time of initial presentation in infancy and supplemental parenteral cobalamin was started empirically thereby avoiding ill effects associated with delayed diagnosis, yet the definitive diagnosis could only be established 6 years after the initial presentation. Due to delayed definitive diagnosis case presentation, investigations, treatment and follow-up will be discussed at various time points—at initial presentation (2 months of age), acute deterioration on cessation of cobalamin (at 18 months) and at the time of definitive genetic diagnosis (6 years).

CASE PRESENTATION

This 6-year-old male child was born to Indian parents with third degree consanguineous marriage. He was first evaluated at age of 2 months when he presented with chronic diarrhoea and failure to thrive. He was on exclusive breast feed. There was no history of jaundice, blood loss or any previous blood component transfusion. He was developmentally normal. On examination, his weight was 4 kg (birth weight 3.5 kg) and head circumference was 40 cm (0 to −1z). He was noted to have pallor and knuckle hyper-pigmentation. There was no dysmorphism, icterus or organomegaly. Neurological examination was normal.

INVESTIGATIONS

At initial presentation, complete blood count (CBC) revealed bicytopaenia with haemoglobin (Hb): 54 g/L (107–171), Total Leucocyte Count (TLC): 8.5×10^9/L (5–19.5) with absolute neutrophil count of 3.3×10^9/L (1.5–8.5), platelet count: 137×10^9/L (150–400), Mean Corpuscular Volume (MCV): 108 fL (91–112) and Mean Corpuscular Hb (MCH): 33 pg/cells (27–36). Peripheral blood film was showing macrocytic Red Blood Cells (RBCs), hyper-segmented neutrophils with slightly reduced platelets. Corrected reticulocyte count was 1% and serum bilirubin was 5.1 µmol/L (<17) suggesting RBC production defect. Other investigations to look into aetiology of bicytopaenia revealed lactate dehydrogenase: 752 U/L (100–250), normal Hb-High Performance Liquid Chromatography (HPLC), serum ferritin: 130 pmol/L (112–450) and negative stool for occult blood . Serum vitamin B_{12} levels were 580 pmol/L (147–664), serum folate levels were 41.36 nmol/L (11.3–47.6), urinary spot MMA (qualitative) was elevated and plasma homocystine levels were 29.45 µmol/L (3.7–13.90).

Bone marrow examination revealed megaloblastic changes and dysplasia in erythrocytic and megakaryocytic lineage with no blasts.

In the intervening period parents took multiple consultations and he was extensively and repeatedly evaluated with a differential diagnosis of Fanconi's anaemia, congenital dyserythropoietic anaemia, severe combined immunodeficiency, intrauterine infections and leukaemia. A karyotype showed 46 XY with no increase in chromosomal breaks in stress cytogenetics. Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus immunoglobulin titres were negative. Serum immunoglobulin profile was normal. Tandem mass spectrometry (TMS) showed mild elevation of C3 acyl carnitine. Holotranscobalamin (HoloTC) levels were not available.

At 6 years of age, when he first presented to our centre, after reviewing the history and

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investigations, which revealed all stigmata of vitamin B_{12} deficiency with repeated normal serum B_{12} levels, a diagnosis of TC deficiency was thought of. Parents were counselled regarding HoloTC test but denied and opted for definitive genetic diagnosis. A targeted next generation sequencing was done, which detected a homozygous nonsense variation in exon 8 of the TCN2 gene (chr22:g.31019043C>T), that results in a stop codon and premature truncation of the protein at codon 399 (p.Arg399Ter).

TREATMENT

At the time of initial presentation on the basis of available investigations he was diagnosed as congenital megaloblastic anaemia (suspected metabolic disorder). He was managed with one packed cells transfusion, 1000 µg of intramuscular cobalamin (cyanocobalamin) weekly for 6 months and subsequently monthly.

At 18 months of age, monthly injections were stopped for around 3 months when the family shifted and consulted a new physician. Child started having irritability and stopped ambulation, Hb also dropped to 50 g/L, requiring two packed cells transfusions. He improved when monthly intramuscular cobalamin was restarted.

After definitive diagnosis of TC deficiency at our centre, parents were advised to continue child on monthly doses of intramuscular cobalamin and genetic counselling was offered.

OUTCOME AND FOLLOW-UP

Index child had a dramatic response to parenteral cobalamin therapy started at the time of initial presentation. At 4 months of age, his weight was 8 kg (0 to +1z), diarrhoea had resolved, Hb had risen to 107 g/L with normal MCV and platelet count of 2.4×10^9/L .On follow-up he was asymptomatic and attaining growth and developmental milestones.

After transient cessation of parenteral therapy at 18 months of age, recurrence of neurological and haematological symptoms was controlled once he was restarted on parenteral cobalamin. He was having normal haematological parameters and was attaining normal growth and development subsequently.

After definitive diagnosis of TC deficiency at our centre, parents were counselled and advised to continue child on monthly doses of cobalamin. Patient is on follow-up for last 1 year with CBC and plasma homocystine levels three monthly. He is having all haematological parameters and plasma homocystine levels within normal limits. Urinary MMA is not being monitored due to non-availability of quantitative test. He has normal anthropometry (weight: 23 kg (0 to +1z), height: 118 cm (0 to +1z)) and is developmentally normal.

DISCUSSION

Megaloblastic anaemia in infancy is rare. Infantile presentation of B_{12} deficiency is associated with maternal B_{12} deficiency, maternal subclinical pernicious anaemia, cblC disorders.[4] TC deficiency is a rare cause of early onset megaloblastic anaemia with reversible clinical manifestations if timely therapy is initiated. Index child had a classical presentation of TC deficiency with bicytopaenia manifesting in early infancy. CBC, bone marrow examination, high plasma homocystine, high urinary MMA and other supporting investigations suggested a possibility of B_{12} deficiency; however, serum B_{12} levels were repeatedly normal. Despite high index of suspicion and enough clinical and lab evidences, normal serum B_{12} levels and probably not readily available HoloTC and genetic tests at the time of initial presentation delayed the definitive diagnosis. Relatively easier and cheaper availability of genetic tests made a definitive diagnosis feasible in index child after 6 years of initial presentation.

The transcobalamin–vitamin B_{12} complex is called HoloTC. HoloTC is the metabolically active cobalamin as it promotes the uptake of cobalamin by all cells via specific receptors. HoloTC is undetectable in conditions like TC deficiency where there is a falsely high cobalamin level.[5] HoloTC was not done in index child due to non-availability during initial presentation and was offered during the time when definitive genetic diagnosis was made but was denied by parents. A delay in diagnosis of TC deficiency is associated with life threatening complications like transfusion dependant anaemia, symptomatic thrombocytopaenia, opportunistic infections, severe failure to thrive and developmental delay due to neuropathy, myelopathy and retinal degeneration.[6 7] In search of a definitive diagnosis multiple differential diagnoses were considered leading to avoidable investigations, financial burden and anxiety to the family which was compounded by therapy interruption leading to resurfacing of symptoms. Thereby reiterating that a high index of suspicion should always be complimented with an effort for definitive diagnosis in the best interest of patient because an empirical therapy will always be subjected to scrutiny once the patient comes in contact with a different physician.[8]

The TCN2 gene is located on chr 22q12.2 and has 427 codons. Most reported mutations in TCN2 gene are deletions or insertions resulting in frameshifts. Nonsense mutations, point mutations and polymorphic variants are also described.[7] Index child has a homozygous nonsense variation in exon 8 of the TCN2 gene (chr22:g.31019043C>T) that results in a premature stop codon and truncation of the protein at codon 399 (p.Arg399Ter) due to loss of C-terminal of 29 amino acid of TC. The reduced affinity of truncated protein for cobalamin or for the receptor may explain clinical manifestations. This mutation have been described earlier as well in two siblings of Albanian ethnicity.[9 10]

There are no guidelines as to how one should treat TC deficiency with respect to form (hydroxycobalamin vs cyanocobalamin), dose, mode of administration (intramuscular vs oral), frequency of administration (weekly vs monthly), duration of administration of cobalamin and monitoring modalities during follow-up. Lifelong parental preparation at 1000 µg with weekly schedule is preferred.[7] Index child was empirically treated with monthly doses of 1000 µg of intramuscular cobalamin and responded dramatically. While cessation of parenteral cobalamin therapy made cytopaenia and neural regression recur and could only be controlled with restarting monthly cobalamin. Index case may support a monthly rather than weekly administration of cobalamin, thereby leading to less frequent visits to medical facility.

In view of severe but reversible nature of systemic effects which includes pancytopaenia, immune deficiency and neuroregression, there is a case for newborn screening (NBS) for TC deficiency. It has been shown that elevation of C3 acyl-carnitine may help as an NBS tool.[11] However the reports are inconsistent.[7] Index child had mild elevation of C3 acyl- carnitine in TMS screening. More consistent screening tests and cost-effective analysis are required before advocating NBS for a rare disorder like TC deficiency.

Contributors SK did the literature search, established definitive diagnosis, manuscript writing, management and follow-up of the patient. SuKP and SaKP were instrumental in final proof reading of manuscript and management and follow-up of the child.

Learning points

- Transcobalamin deficiency should be considered when signs of vitamin B_{12} deficiency are present with normal serum B_{12} levels.
- Awareness of this treatable condition with reversible nature of clinical manifestations with timely therapy helps in avoiding deleterious effects of delayed diagnosis.
- A definitive diagnosis by relevant genetic/molecular analysis will lead to the holistic management of the patient including a genetic counselling, especially in disorders which manifest in early infancy.

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