Congenital Hypotransferrinemia, an Unusual Cause of Iron Deficiency Anemia: Report of Two Cases

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Abstract Hereditary hypotransferrinemia is a very rare cause of iron deficiency anemia in childhood characterized by microcytic hypochromic anemia refractory to iron therapy and concomitant iron overload. Regular plasma infusion to replace the deficient transferrin molecule is the therapeutic option. We report two cases; both presented with refractory anemia requiring blood transfusions and responded to monthly fresh frozen plasma replacement.

Keywords Congenital atransferrinemia · Hypotransferrinemia · Iron deficiency anemia

Introduction

Congenital atransferrinemia (CAT) and hypotransferrinemia are rare entities with only 16 reported cases till date [1–3, 5]. Inheritance is autosomal recessive with mutations in the *TF* gene (3q21) encoding transferrin (TF) [4]. They present with microcytic, hypochromic anemia, due to TF deficiency. Onset of the disease is usually in infancy or early childhood with pallor, fatigue, anorexia, irritability, growth retardation and recurrent infections. Despite anemia, there is iron overload that can lead to liver cirrhosis, heart failure, and splenomegaly.

Case Report 1

A 6-year-old male born of a non-consanguineous marriage presented with a 4-year history of anemia requiring four blood transfusions till date and multiple trials of hematinics. Examination revealed pallor and coronal hypospadias (asymptomatic). He was developmentally normal and adequately immunized. Liver function test (LFT), renal function test (RFT) and serum lead levels were normal. Serologic markers for hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), toxoplasma, and cytomegalovirus were negative.

Hematological and iron profile showed microcytic hypochromic anemia with hyperferritinemia and low serum iron. Tables 1 and 2 only four transfusions could not account for the observed high serum ferritin (1413 µg/L). The differential diagnoses of hemolytic anemia, congenital dyserythropoietic anemia and aceruloplasminemia were ruled out. A diagnosis of congenital hypotransferrinemia was suggested based on non-response to repeated trials of oral haematinics and raised serum ferritin; confirmed by low level of TF (70 mg/dL; normal range 203–362 mg/dL by immunoturbidimetry) in patient and lower than normal levels of TF in the asymptomatic parents (160 and 172 mg/dL respectively). Normal blood sugar, LFT and echocardiography ruled out organ involvement secondary to iron overload.

The patient has responded to treatment regimen of monthly infusions of fresh frozen plasma (FFP), with an increase of reticulocyte count to 6% at 2 weeks, Hb rise to 12.4 mg/dL at 1 month and decline of serum ferritin to 903 µg/L after 12 months. Molecular studies could not be performed due to non-availability of the same in our setup and financial constraints of the patient. Iron chelation was not initiated due to continued decline of serum ferritin. He

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Table 1 Hemogram, peripheral smear and bone marrow finding of patient 1 and 2

	Hb (g/L)	RBC counts ($\times 10^{12}$ L)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW-CV (%)	Corrected reticulocyte count (%)	Peripheral smear	Bone marrow aspiration and biopsy
Case 1	62	3.15	58	19.4	297	22.6	1.1	Microcytic hypochromic	Cellular, erythroid hyperplasia, no dysplasia
Case 2	52	3.46	61	19.1	326	16.4	1.3	Microcytic hypochromic	Cellular, mild erythroid hyperplasia, no dysplasia

Hb hemoglobin, *RBC* red blood cell, *MCV* mean corpuscle volume, *MCHC* mean corpuscle hemoglobin concentration, *RDW-CV* red cell width-coefficient variant

Table 2 Iron studies and other hematological test performed to diagnose etiology of anemia

	Iron ($\mu\text{g/dL}$) (65–176)	TIBC ($\mu\text{g/dL}$) (240–450)	Tf saturation (%) (16–50)	Ferritin ($\mu\text{g/L}$) (45–160)	TF (mg/dL) (203–360)	Cerolo-plasmin (mg/dL) (15–60)	HPLC	G6PD	Coomb's test	HEMPAS test
Case 1	10	381	3	1413	70	Normal	Normal	Normal	Negative	Negative
Case 2	9	360	24.46	2072	75	NA	Normal	Normal	Negative	Negative

TIBC total iron binding capacity, *TF* transferrin, *NA* not available, *HPLC* high performance liquid chromatography, *G6PD* glucose 6 phosphate dehydrogenase, *HEMPAS* hereditary erythroblastic multinuclearity with positive acidified serum lysis test

is in follow-up with the pediatric surgeons also for hypospadias.

Case Report 2

A 4-year-old girl, born of non consanguineous marriage was apparently well till 10 months of age, when her parents noticed pallor and lethargy with poor oral intake. She had received hematinics for 3 years and four transfusions of packed red blood cells. Examination revealed pallor and mild hepatosplenomegaly. However no icterus, facial dysmorphism, skeletal abnormalities or skin lesions was noted. The child was developmentally normal and immunized for age. LFT and RFT were normal. Viral serology was negative.

A diagnosis of congenital hypotransferrinemia was suspected on the basis of refractory anemia not responding to hematinics, low serum TF level with an increased serum ferritin (Tables 1, 2), further confirmed by low serum TF level in the parents (156 and 180 mg/dL respectively). Other common causes of anemia requiring transfusion support were excluded. The patient was advised regular FFP transfusion, but was lost to follow-up.

Discussion

Heilmeyer et al. [1] first described congenital atransferrinemia in 1961 in a 7-year-old girl who died of heart failure. Aslan et al. [2] reported a new case and reviewed ten previously reported cases. Till date only 16 cases of

CAT have been reported from 14 families [1–3, 5]. Congenital atransferrinemia or hypotransferrinemia is due to autosomal recessive mutation in the TF gene located on chromosome 3q21 encoding a single peptide chain glycoprotein TF; synthesized predominantly in liver. TF binds and delivers trivalent iron to erythroid precursors for synthesis of hemoglobin. Deficiency of TF leads to reduced hemoglobin synthesis and anemia, but with excess iron stored in peripheral tissues (secondary hemochromatosis) [4]. Manifestations of severe anemia develop in infancy or early childhood, i.e. pallor, fatigue, anorexia, irritability, tachycardia, systolic murmur, hepatomegaly, growth retardation and recurrent infections. Iron overload can lead to hepatic fibrosis, cirrhosis, arrhythmias, heart failure, and endocrinopathies like diabetes mellitus, secondary hypoparathyroidism and hypothyroidism.

Hypospadias has been reported with other cases of hypotransferrinemia and could be explained by fetal hypoxia leading to developmental anomaly [5].

The diagnosis of atransferrinemia or hypotransferrinemia may be suspected in cases with moderate to severe anemia, low serum iron, transferrin saturation, TIBC, TF level; but with high serum ferritin. The bone marrow shows erythroid hyperplasia with decreased iron stores. Hepatomegaly, due to hemosiderosis and fibrosis may be noted in some cases. Diagnosis is confirmed by molecular genetic testing for mutation in the TF gene. Genetic counseling is available. Treatment usually involves infusions of FFP or purified apotransferrin that removes excess iron and replenishes the TF levels. Monthly phlebotomy or iron chelation may be done in severe iron overload. Treatment is life-long and regular follow-up is recommended [6].

Our patients need to be in long-term follow-up to monitor the effectiveness of therapy and manage iron overload. Hypotransferrinemia though rare should be ruled out in all case of treatment refractory microcytic hypochromic anemia.

Compliance with Ethical Standards

Conflict of interest The corresponding authors and all other authors have no conflict of interest, no drugs were used.

Ethical Standards The patients gave consent for all tests and treatment provided. All procedures performed were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration. All patient details are anonymised in this case report.

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