Refractory anemia : Think about genetic iron metabolism defects!

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ABSTRACT

Introduction : Inherited iron metabolism defects are usually expressed by hypochromic microcytic anemia. They are very exceptional and often misdiagnosed by clinicians. We aimed to report an exceptional case of congenital hypotransferrinemia revealed by a precocious anemia.

Case report : We report the case of a seven-months-old girl born of a second degree consanguineous marriage. She was referred for persistent anemia since one month of age. She had received iron supplementation for four months and two transfusions of packed red blood cells. Physical examination revealed pallor. However no icterus, facial dysmorphism, skeletal abnormalities or skin lesions was noted. Complete blood count revealed a hypocromic microcytic anemia at 6g /Dl. Serum ferritin and serum were respectively of 2500 ng / mL and 1.5 µmol /L. The diagnosis of congenital hypotransferrinemia was suspected on the basis of refractory anemia, low serum iron level with an increased serum ferritin. Serum transferrin level was of 0.15 g /L. (Normal range 1.8 -3.9 g/L). Differential diagnosis such as thalassemia, aceruloplasminemia and sideroblastic anemia were ruled out. DNA analysis of the serum transferrin gene revealed a mutation in exon 4, a G-->A transition at cDNA 410(Cys137Tyr). Given the non-availability of apo-transferrin, therapeutic management was based on regular infusions of fresh frozen plasma and iron chelation.

Conclusions : Although congenital atransferrinemia was described approximately half a century ago, it is very uncommon and only a few patients have been characterized on a molecular basis. Hypotransferrinemia though rare should be ruled out in all case of treatment refractory microcytic hypochromic anemia.

Keywords : Atransferrinemia; Iron overload; Microcytic anemia

INTRODUCTION :

Inherited disorders of iron metabolism develop as a result of disruption of systemic iron homeostasis. Due to their scarcity, these conditions are often unrecognized by clinicians.
Congenital atransferrinemia or hypotransferrinemia is a very rare autosomal recessive disorder, characterized by a deficiency of transferrin, resulting in a severe hypochromic, microcytic anemia in early infancy. Only few cases are reported in literature to date.
Our objective was to report an exceptional case of congenital hypotransferrinemia revealed by a precocious refractory anemia in order to contribute to the study of this rare condition

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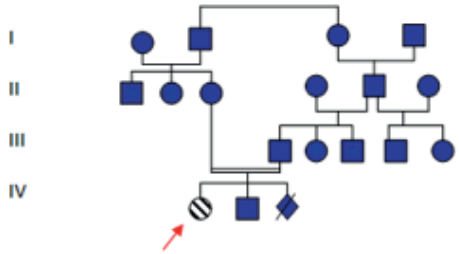
CASE REPORT :

We report the case of seven months-old girl who was followed for anaemia since one month of age. She was born of second degree consanguineous healthy parents. None of the relatives had been known to have anaemia or other hematologic disorders. Figure 1 shows the family pedigree.

Figure 1 : The family pedigree showing a case of hypotransferrinemia after three healthy generations



She was born from a full-term pregnancy with a birth weight of 3100 grams. She was discharged from maternity on the second day of life with no history of bleeding or neonatal anemia. Subsequently, she was apparently well until one month of age, when her parents noticed pallor and lethargy with poor oral intake. A complete blood count (CBC) was performed showing a hemoglobin level of 5 g/dL. She received a transfusion and iron supplementation which was regularly and correctly taken. Three months later, the patient was still lethargic and the pallor appeared again. Haemoglobin level was of 4.4 g/dL. She received her second packed red blood cells transfusion. At that moment she was still taking iron supplementation which was stopped one month later. Otherwise, the patient had no history of gastrointestinal bleeding, hemoptysis or regurgitation. Thereafter, the infant was referred to our department at the age of 7 months for refractory anemia. On physical examination, she had a poor weight gain with weight at 5400 grams (-2.5 standard deviations). She had a normal height at 70 cm. She was very pale without jaundice. She had no dysmorphia and cardiovascular and pulmonary examinations were normal. The liver edge was palpable three centimetres below the right costal margin. There was no splenomegaly neither palpable lymph nods. CBC showed haemoglobin level of 5.5 g/dL. Mean corpuscular volume was of 56 femtoliters. Mean Corpuscular Hemoglobin and mean cell hemoglobin concentration were respectively 19 pg and 23 g/dL. Reticulocytes count was of 0.5 %. Leukocytes and platelets counts were normal. Hemoglobin electrophoresis was normal excluding thalassemic syndrome (HbA1=97%, HbA2=3%, HbF=0). Serum ferritin and serum iron were respectively of 2500ng / mL and 1.5 µmol /L. The erythrocyte sedimentation rate was 8 mm at first hour and C reactive protein was negative. Liver tests including transaminases were within normal ranges. There was no occult blood on the stool tests. The diagnosis of inherited iron metabolism defect was suspected on the basis of refractory anemia, low serum iron level with an increased serum ferritin. The microscopic bone marrow examination did not show any sideroblasts excluding the possibility of sideroblastic anemia, which is usually expressed by hyperferrinemia and hyposideremia. Aceruloplasminemia was also ruled out based on the normal rate of serum ceruloplasmin. Thereafter, serum transferrin was performed and was very low at 0.15 g/L (normal range 1.8-3.91g/L). It was of 3.4g/L in a healthy volunteer control. Thereby the diagnosis of hypotransferrinemia was made. It was definitely confirmed by DNA analysis of the transferrin gene which revealed a mutation in exon 4, a G-->A transition at cDNA 410(Cys137Tyr). Due to the non-availability of apo-transferrin, the patient was managed by monthly infusions of fresh frozen plasma and iron chelation by deferasirox 25 mg/kg/day with an increase of reticulocyte count to 7 % and hemoglobin to 11 mg/dL at 3 month and decline of serum ferritin to 930 g/L after 16 months.

The table 1 summarizes the evolution of biological parameters and the prescribed therapeutics before and after making the diagnosis of hypotransferrinemia.

Table 1 : The evolution of biological parameters according to prescribed therapeutics for hypotransferrinemia

Age	1 month	4 months	7 months	8 months	10 months	15 months	24 months
Hemoglobin (g/dl)	5	4.4	5.5	7.2	11	10.8	11.3
Reticulocytes (%)	-	-	0.5	-	7	3	4
Leukocytes count (cells/mm^3)	8 100	9 560	13 400	8 770	8 790	11 800	13 590
Platelets count (cells/mm^3)	263 000	350 000	425 000	519 000	283 000	487 000	475 000
Serum ferritin (ng/mL)	-	-	2500	3100	1000	1200	930
Serum iron (µmol/L)	-	-	1.5	-	-	-	-
Serum transferrin (g/L)	-	-	0.15	-	-	-	0.13
therapeutics	Blood transfusion + Iron supplementation	Blood transfusion + Iron supplementation	Blood transfusion	Plasma + iron chelation	Plasma + iron chelation	Plasma + iron chelation	plasma

DISCUSSION :

The glycoprotein transferrin (siderophilin) is a βglobulin with a molecular weight of about 90,000. Its normal serum level ranges from 200 to 300 mg/100 mL. One molecule of transferrin binds two molecules of trivalent iron, thus playing an important role in iron transfer [1]. Acquired hypotransferrinemia is well Known and it is usually observed in infections by aggregation of transferrin in the inflammatory region, hepatic disorders decreasing the synthesis of transferrin and malignant tumors [1, 2]. In the presented case we excluded all causes of acquired hypotransferrenimia as soon as we noticed low serum transferrin.

On the other hand, only few cases of congenital atransferrinemia have been reported.

The clinical spectrum of congenital atransferrinemia is variable [3-6]. In the case reported by Heilmeyer [7], the diagnosis of severe hypochromic anemia was made three months after birth. Management by hematinics was ineffective. She had also growth retardation and repeated infections. Blood transfusion was required every 3 months, and death occurred at the age of 7 year as a result of severe iron overload. In contrast, Goya and Hayashi's patient had late onset of the disease [8]. The patient was doing well until he had a sudden fainting attack at the age 7 years. This could be explained by residual secretion of transferrin or variability in the severity of the disease depending on the causal mutation. For the moment, the correlation between genotype and phenotype remains difficult to study given the scarcity of the disease. For clinicians, the biological profile associating microcytic anemia with low serum iron and hyperferritinemia should be suggestive of iron metabolism disorder since the reserves are existing or increased but iron is paradoxically unrelated to the bone marrow [1, 9]. In these cases, the evoked diagnoses are mainly aculoplasminemia, sideroblastic anemia and hypotransferrinemia. The diagnosis of atransferrinemia or hypotransferrinemia may be suspected in cases with moderate to severe anemia, low serum iron, transferrin saturation, and serum transferrin 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 transferrin gene [1, 5,7]. The main treatment of congenital atransferrinemia is transferrin infusions [10]. There is no protocol for frequency and doses. In fact, transferrin stimulates the hemopoiesis, increasing red cell production and the duration of the effect to the life-span of the erythrocyte. Neither side effects nor reduction in the effectiveness of transferrin administration were noticed. It is obvious that the prognosis of the disease depends on the degree of iron overload. Severe hemosiderosis has been reported in all patients, except the case reported by Goya and Hayashi [8]. In fact, deficiency was observed in this patient for about 4-5 years, after which it gradually recovered. Although there is no satisfactory explanation of the recovery, some internal stimuli, including hormonal activities, may have induced transferrin biosynthesis. Given the non-availability of apo-transferrin, our patient was successfully managed with monthly fresh frozen plasma transfusions and iron chelation which were safe and effective.

CONCLUSION :

We reported a particular observation in view of the rarity of hypotransferrinemia, the delayed diagnosis and the successful management by plasma transfusions regarding the non-availability of apo-transferrin. Finally, clinicians should consider iron metabolism defects in cases of anemia with too early onset or unusual evolution to make an earlier diagnosis and thus improve the prognosis of the disease.

FOOTNOTES:

CONSENT : Written informed consent was obtained from the patient for publication of this case report.

AUTHOR CONTRIBUTION : Salem Yahyaoui wrote the paper. All authors provided care and follow-up for the patient.

FUNDING : No funding has been used for this research.

ETHICAL APPROVAL : No ethical approval has been applied for this case report study, only the written and oral consent by the patient's parent.

GUARANTOR : Salem Yahyaoui has full responsibility for the work.

CONFLICTS OF INTEREST : No conflict of interest.

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REFERENCES :

[1] Kostas P. Inherited Disorders of Iron Overload. Front Nutr 2018; 5: 103-18.

[2] Hayashi A, Wada Y, Suzuki T, Shimizut A. Studies on Familial Hypotransferrinemia: Unique Clinical Course and Molecular Pathology. Am. J. Hum. Genet 1993; 53:201-13.

[3] Nagahide G, Sumio M, Saburo K, Bun I U. A Family of Congenital Atransferrinemia. Blood 1972; 40 (2): 119-25.

[4] Randy L, Hamill L, Woods JC, Bruce A. Congenital atransferrinemia: A case report and review ofthe literature.Am J Clin Pathol 1991;96:2155–88.

[5] Dinesh CH, Bhavna D, Tulika S, Pravas M, Divya B, Manoranjan M, Pati HP Congenital Hypotransferrinemia, an Unusual Cause of Iron Deficiency Anemia: Report of Two Cases. Indian J Hematol Blood Transfus 2017; 33(3):402–4.

[6] Aslan D, Crain K, Beutler E (2007) A new case of human atransferrinemia with a previously undescribed mutation in the transferring gene. Acta Haematol 2007; 118:244–47.

[7] Heilmeyer L, Keller W, Vivelle O, Keiderling W, Beteke K, WoehlerF et al. Congenital atransferrinemia in a 7-year-old girl. Dtsch Med Wochenschr 1961;15;86:1745-51.

[8] Goya N, Miyazaki S, Kodate S, Ushio B. A family of congenital atransferrinemia. Blood. 1972;40(2):239-45..

[9] Shamsian BS, Rezaei N, Arzanian MT, Alavi S, Khojasteh O, Eghbali A. Severe hypochromic microcytic anemia in a patient with congenital atransferrinemia. Pediatr Hematol Oncol 2009; 26:356–362.

[10] Kawakami T, Sone Y, Numajiri S, Sakata T. Replacement therapy for a patient with congenital atransferrinemia—therapeutic effect of apotransferrin. Rinsho Ketsueki 2001;22:1708–13.