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The Wide Clinical Spectrum of Raised Fetal Hemoglobin in Adults

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ABSTRACT

Fetal hemoglobin (HbF) is found in infants up to 6 months. It is a normal physiological phenomenon. However in adults, in the absence of hemoglobin A (HbA) in thalassemic syndromes, HbF is raised even to 98%. However, presence of HbF does not always prevent symptoms. There is a wide clinical spectrum of disease. Some patients are asymptomatic as in delta-beta-thalassemia and hereditary persistence of fetal hemoglobin (HPFH) and some have severe symptomatic disease as in beta-thalassemia.

Keywords: Beta-thalassemia, delta-beta-thalassemia, HPFH, HbF, HbA, red cell indices

The thalassemic syndromes are inherited disorders of globin synthesis and present as hemolytic anemia. The reduced supply of globin causes hypochromia and microcytosis. In beta-thalassemia, there is unbalanced accumulation of alpha-chain and reduction of beta-chain. This is to some extent corrected by gamma-chain (fetal hemoglobin [HbF]). However, the clinical severity varies widely even though HbF replaces the hemoglobin A (HbA).

We are presenting two cases of raised HbF with widely varying clinical picture.

CASE REPORTS

Case 1

A 13-year-old boy presented with history of fever for 3-4 days, associated with abdominal pain, along with anorexia, nausea and generalized fatigue since a week. Patient's parents also noticed icterus and yellowish discoloration of urine since 3-4 days. On examination, patient was anemic, icteric with splenomegaly.

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Investigations

Hemoglobin (Hb) - 10.1 g/dL, mean corpuscular volume (MCV) - 69.6 fl, platelet - 2.83 lakhs, erythrocyte sedimentation rate (ESR) - 40 mm/hr; Mentzer index - 15.13, reticulocyte count - 0.6%.

Peripheral smear - microcytic hypochromic picture along with many target cells and few elliptocytes.

Hyperbilirubinemia was mainly indirect (total - 5.2 mg/dL); serum glutamic pyruvic transaminase (SGPT) - 133 IU/L.

USG abdomen - Splenomegaly, minimal ascites, distended gallbladder with sludge.

Viral markers - negative; Coombs test - negative; NESTROFT - positive; Hb electrophoresis - 98.7% HbF, 1.3% HbA2.

Past History

Patient had blood transfusion three times in the last 6 years and his lowest Hb was 5 g/dL in 2009 when he took treatment for the first time. He was given 2 pints of packed cells on first occasion. Later on, after 1-2 years interval, he was again transfused when minimum Hb was 7 g/dL. Every time patient had indirect hyperbilirubinemia and predominance of HbF on Hb electrophoresis. Coombs and glucose-6-phosphate dehydrogenase (G6PD) was negative. Reticulocyte count was 3-6%. On further follow-up, Hb was 8-11 g/dL.

On further analysis of patient's parents: Father was diagnosed as thalassemia minor and mother was diagnosed as hereditary persistence of fetal hemoglobin (HPFH). Parents never required transfusion and since last 2 years patient had not required transfusion.

Case 2

A 33-year-old male patient presented to OPD with chief complaint of abdominal pain in left hypochondrium, low intensity in nature, nonradiating since 12 days. There was no complaint of nausea or vomiting or any previous blood transfusion. Patient was conscious, oriented, hemodynamically stable, nonicteric and nonanemic. On abdominal examination, mild splenomegaly without tenderness was noted.

Investigations

White blood cell (WBC) - 9,400 (N_{62},L_{30},M_7,E_0,B_0), red blood cell (RBC) - 6.09 lakhs, platelet - 2.88 lakhs, Hb - 12.4 g/dL, hematocrit - 37.5%, mean corpuscular hemoglobin (MCH) - 18.7 pg/dL, MCV - 61.6 fl/dL, mean corpuscular hemoglobin concentration (MCHC) - 30.4%, red blood-cell distribution width (RDW) - 45.7%, ESR - 22/hr, reticulocyte count - 1%, Mentzer index - 12.3, NESTROFT - positive. Peripheral smear showed microcytic hypochromic anemia.

Serum creatinine - 0.5 mg/dL, serum urea - 19 mg/dL, random blood sugar (RBS) - 89 mg/dL, SGPT - 54 mg/dL, lactate dehydrogenase - 193.8 mg/dL.

Serum bilirubin (total - 1.2, indirect - 1.0, direct - 0.2 mg/dL), viral markers - negative.

USG - Hepatosplenomegaly; liver 14.5 cm and spleen 15.3 cm.

Hb electrophoresis - 100% HbF on HPLC and capillary method.

DISCUSSION

Hemoglobin A is the major normal adult Hb. It consists of heme + globin. Globin consists of two alpha chains and two beta chains. HbF is the major hemoglobin of the fetus. It consists of two alpha chains and two gamma chains. HbA2 consists of two alpha chains and two delta chains. It accounts for 1.5-3.5% of normal adult Hb. Thalassemia is an inherited disease causing impairment of globin chain production. In thalassemias, globin chains of normal structure are produced at a decreased rate. The beta-thalassemias and their associated biochemical and molecular defects are given in Table 1.

Beta-thalassemia refers to decreased production of beta chains. This is compensated by increased production of delta chains. Hence, there is an increase in HbA2. However, it is never more than 12%. The beta-thalassemias are clinically classified as beta-thalassemia major, a severe and transfusion-dependent form; beta-thalassemia intermedia with less severe symptoms; and beta-thalassemia minor or trait without clinical symptoms but with hematological abnormalities (Table 2). With an absence (β^0) or marked decrease (β^+) in beta-chain production, there is an excess of

Table 1. Beta-thalassemias and their Associated Biochemical and Molecular Defects

	Typical DNA defect	β-chain	δ-chain	γ-chain	HbF distribution	α: Non-α-globin imbalance
β^+-thalassemia	Mutation	↓	+	+	Heterocellular	+++
β^0-thalassemia	Mutation	0	+	+	Heterocellular	++++
δβ-thalassemia	Deletion	0	0	+++	Heterocellular	++
HPFH	Deletion	0 or ↓	0	++++	Pancellular	+

Table 2. Major Categories of Beta-thalassemia Syndromes

Syndrome	Genotype	Clinical features	Hemoglobin pattern
Homozygous states			
β^+-thalassemia	β^+/β^+	Thalassemia major or intermedia	↓↓ HbA, ↑↑ HbF, variable HbA2
β^0-thalassemia	β^0/β^0	Thalassemia major	>95% HbF, rest HbA2
$\delta\beta^0$-thalassemia	$\delta\beta^0/\delta\beta^0$	Thalassemia intermedia	100% HbF
Hb Lepore	Lepore/Lepore	Thalassemia major	85% HbF, 15% Hb Lepore
Heterozygous states			
β^+-thalassemia	β^+/β	Thalassemia minor	HbA, ↑ HbA2, ±↑ HbF
β^0-thalassemia	β^0/β	Thalassemia minor	HbA, ↑ HbA2, ±↑ HbF
$\delta\beta^0$-thalassemia	$\delta\beta^0/\delta\beta$	Thalassemia minor	HbA, 5-20% HbF, ±↓ HbA2
Hb Lepore	Lepore/β	Thalassemia minor	HbA, ↑ HbF, ↓ HbA2,10% Hb Lepore

alpha chains, which precipitate and cause ineffective erythropoiesis and form toxic inclusion bodies that kill erythrocytes and cause hemolytic anemia. Thalassemias are also classified as homozygous and heterozygous states.

Clinical findings include jaundice, leg ulcers, gall stones, high output cardiac failure and splenomegaly evident in early childhood. There is a prominence of frontal bones, cheek bones and jaws due to extreme bone marrow hyperplasia, presenting with characteristic chipmunk facies.

X-rays findings of thinned cortex of long and flat bones and thickening of skull with osteoporosis (hair on end appearance) are seen. Growth is stunted. Most patients require regular transfusions due to profound anemia and iron over loading occurs.

Unlike most hemolytic diseases, the anemia is microcytic and hypochromic. In β^0-thalassemia (homozygous) HbA is absent, HbF is as high as 98% and HbA2 is 2%. In β^+-thalassemia (heterozygous), HbF is 60-95%, HbA is present but HbA2 ratio to HbA is always increased.

In delta-beta-thalassemia, beta and delta chains are not produced and there is a significant increase in HbF. In the homozygous state, Hb consists only of HbF. The heterozygous state is similar to mild beta-thalassemia trait except that HbA2 is not increased or is even reduced and HbF is increased. Clinically, homozygous delta-beta-thalassemia behaves as a mild form of beta-thalassemia intermedia with Hb level of 10-13 g/dL, mildly thalassemic red cell indices and mild hepatosplenomegaly. The mild phenotype is the result of increased production of gamma-chain, which compensate to some degree for lack of beta chains.

HPFH - In this condition, there is persistence of HbF in adults without significant hematologic abnormalities or clinical illness.

The rise in HbF in adults presents with a wide clinical spectrum. In one end of the spectrum, in β^0-thalassemia, HbF may be raised to even more than 95% with the rest HbA2 and absent HbA. This presents in childhood, clinically as homozygous β^0-thalassemia major, with profound anemia, microcytic hypochromic picture in peripheral smear, red cell indices of thalassemia. Target cell, poikilocytosis, Howell-Jolly bodies and anisocytosis are seen. The reticulocyte count is less elevated than expected for degree of anemia because of destruction of erythroid precursors in the marrow. Intramedullary destruction of Hb (ineffective erythropoiesis) is markedly increased. Extramedullary erythropoiesis occurs and patients die by the third decade. The raised gamma chains do not compensate for the lack of beta chains by improving clinical outcome.

The other clinical picture is that of delta-beta-thalassemia (homozygous), where HbF is again very high (even 100%). HbA is absent and HbA2 may be absent or present in normal range. But unlike β^0-thalassemia major, it presents clinically as a mild form of beta-thalassemia intermedia. Patients present with above 10 g/dL, mild thalassemic indices and minimal hepatosplenomegaly. The raised gamma chains compensate to high-degree for the lack of beta chains.

At the other end of the spectrum is HPFH, where HbF is raised to nearly 100%. Hb levels are normal, red cell indices are normal and patients are asymptomatic and are apparently healthy. They are usually not diagnosed as they never need treatment and may not visit a hospital.

Both our patients had raised HbF to >98%. However, 1 patient presented with severe anemia in childhood to the extent of requiring 3 blood transfusions with a clinical picture of jaundice, splenomegaly, raised reticulocyte count, Mentzer index of 15.13 and thalassemic red cell indices, HbF 98.7%, HbA2 1.3%, absent HbA and had β^0-thalassemia major.

The other patient was 33 years old; clinically there was no anemia, no icterus, mild splenomegaly, with mild thalassemic red cell indices, reticulocyte count of 1%, HbF 100%, absent HbA and HbA2. He had delta-beta-thalassemia, which presented clinically with mild symptoms of beta-thalassemia intermedia.

CONCLUSION

The carry home message of this presentation is that although HbF is elevated in the absence of HbA after birth, all is not well. The prognosis depends on the clinical picture, which can present as β^0-thalassemia in childhood with early death, but it can also present as delta-beta-thalassemia and HPFH, where they are asymptomatic and lead normal lives.

SUGGESTED READING

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