Hereditary persistence of fetal hemoglobin

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Abstract:
Hereditary persistence of fetal hemoglobin (HPFH) is a benign condition in which significant fetal hemoglobin (HbF) production continues well into adulthood, disregarding the normal shutoff point after which only adult-type hemoglobin should be produced. The percentage of incorrect expression might be as low as 10%–15% or as high as 100% of the total hemoglobin, usually higher in homozygotes than in heterozygotes. The present case is a typical example of homozygous HPFH.

Keywords: Hereditary persistence of fetal hemoglobin, heterozygotes, homozygotes

Introduction
Hereditary persistence of fetal hemoglobin (HPFH) is a condition with significant fetal hemoglobin (HbF) production which continues in adulthood. This is usually caused by mutations in the β- or α-globin gene cluster or the γ promoter gene region. As first discovered in Nigeria by Edington and Lehmann,¹² HPFH has been encountered in people of African descent in Uganda,³ Jamaica⁴,⁵ and in the United States⁶‑¹² and in a single Caucasian family in Greece.¹³ The anomaly has been encountered in the homozygous and heterozygous state. Heterozygotes (up to 30% HbF) have displayed no other abnormality of hemoglobin synthesis (A‑F) or have been heterozygous in addition for hemoglobin S (S‑F), hemoglobin C (C‑F), or thalassemia (Thai‑F). Homozygote: only one person apparently homozygous for the anomaly has been discovered,¹¹ a child of 33 months. In persons with sickle cell disease, high levels of HbF as found in a newborn, or as found abnormally in persons with HPFH, the HbF causes the sickle cell disease to be less severe. In essence, the HbF inhibits polymerization of HbS. A similar mechanism occurs with persons who have sickle cell trait. Approximately 40% of the hemoglobin is in the HbS form while the rest is in normal HbA form. The HbA form interferes with HbS polymerization.¹⁴ Delta beta thalassemia and HPFH constitute a heterogeneous group of disorders characterized by absent or reduced synthesis of adult hemoglobin (Hb A) and increased synthesis of HbF. Coinheritance of these disorders with other beta chain hemoglobinopathies, such as beta thalassemia and the sickle cell (beta s) gene, can result in attenuation of the clinical severity of these hemoglobinopathies owing to the increased Hb F levels. The molecular basis of these disorders is quite heterogeneous and consists of both deletion and nondeletion types of mutations. The characterization of these molecular defects has provided new insights on the structure and function of important regulatory elements that are involved in the normal control of expression of the beta- and gamma-globin genes and in hemoglobin switching.

Case Report
A 50-year-old male, father of a β-thalassemia major patient, reported having HbF, i.e.,
94.90% without any symptoms while being investigated for the thalassemic patient’s family status.

Family history

Wife is a known case of thalassemia minor with the history of three miscarriages. Family has an 8-month live baby with thalassemia major. No other live member (maternal/paternal) was available for the further investigation.

Investigations

Father’s hemoglobin by high performance liquid chromatography (HPLC)/electrophoresis is HbF - 94.90%, Hb A - 2.60%, HbA2 - 2.0%, and others - 0.50%. Hb concentration - 15.10 g% with erythrocytosis (RBC count - 6.37 million/mm3). Child – hemoglobin HPLC/electrophoresis – HbF - 91.60%, Hb A - 6.0%, HbA2 - 2.1%, and others - 0.30%. Mother – reported as β-thalassemia minor.

Discussion

By 6 months of age, a shift from gamma globin to beta globin (HBB) gene expression occurs, reducing the amount of (HbF; α2 γ2) produced so that the major form of hemoglobin present is Hb A (α2 β2). Although residual amounts of Hb F are produced throughout life, the majority of healthy adults have <1% Hb F. HPFH results from mutations within the beta globin gene cluster that alter normal hemoglobin switching. Heterozygotes for HPFH-associated deletions typically have high levels of Hb F (up to 30%) with normal red blood cell indices while homozygous or compound heterozygous, when two deletions associated with HPFH are identified, individuals typically have Hb F levels approaching 100% with mild erythrocytosis. The present case is provisionally diagnosed as homozygous HPFH because HbF is >30% and other hemoglobins, i.e. Hb-S (S-F), hemoglobin C (C-F), and Thalassemia (Thai-F) were absent, that are present in heterozygous HPFH. Cases of heterozygous HPFH were reported from various regions of India15–17 and from overseas in African and Greek descendents.18–20 The prevalence of heterozygous HPFH in African inhabitants is 0.1%.21 To the best of our knowledge, few cases of homozygous HPFH have been reported till date.21,19,20 Hence, the present case is among the rare cases of homozygous HPFH and should be built-in records.

Conclusion

HPFH is an anomaly of hemoglobin production apparently caused by mutant gene that inhibits synthesis of hemoglobin A and Aγ. The above case is a classical example of homozygous HPFH in a 50-year-old healthy asymptomatic male.

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Conflicts of interest

There are no conflicts of interest.

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