Compound Heterozygous Sickle and Thalassemia Trait: A Case Report

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Abstract

Sickle cell disease is a type of hemoglobinopathy, which is fairly common in certain parts of the world. We would like to report an interesting case of a child who was labeled as sickle cell anemia but subsequently turned out to be a case of compound heterozygous sickle cell and thalassemia trait.

Keywords: Sickle cell disease, haemoglobinopathy, thalassemia, hydroxyurea, globin, electrophoresis, HPLC

Introduction

Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Haemoglobinoapthies are resulted due to the abnormalities in these chains. Sickle cell disease is a type of hemoglobinopathy with diverse and variable clinical presentation. The clinical sequel of sickle cell disease is hemolytic anemia and vaso-occlusive crises and chronic progressive organ damage. We would like to report a case which was diagnosed as sickle cell anemia; however, the case turned out to be compound heterozygous sickle cell and thalassemia trait subsequently.

Case Report

Five and a half years old boy, first product of 3rd degree consanguineous marriage, born at term with no significant perinatal history, was admitted as a known case of sickle cell anemia. He had presented at the age of two months with fever and anaemia. Peripheral blood smear at that time had shown sickle cells and hemoglobin electrophoresis had shown HbF-25%, HbA-6.5%, HbA2-4.9% and HbS-63.2% as per the available documents. He was labeled as sickle cell anemia and advised for blood transfusion. However, he had remained apparently asymptomatic till five years of age when he again presented with headache.

At the time of presentation in our hospital, his vitals were all stable. His weight was 13 kg (68% of 50th centile, as per NCHS standards) and height was 104 cm, just above the 3rd centile. General examination revealed pallor and mild icterus. On systemic examination of the abdomen, his liver was palpable 2 cm below right subcostal angle on mid-clavicular line with the span of 11 cm and spleen was palpable 4 cm below left subcostal angle on mid-clavicular line with the span of 12 cm. Rest of the systemic examination was essentially within normal limits.

Considering his unusual presentation of apparent well thriving, his diagnosis was reconsidered and the complete investigation of the entire family was undertaken.

Complete blood picture of the patient's father revealed Hb-12.7 gm%, MCV-58.6 fl, TRBCs- 6.49x10^6/µL, Mentzer's index-9 with microcytic hypochromic cells with mild anisopoikilocytosis and target cells. Sickling test was negative. Hb electrophoresis showed no F

band. High performance liquid chromatography (HPLC) showed HbF-0.9%, HbA-84.9% and HbA2-5.7%. The father was thus diagnosed as a case of beta thalassemia trait.

ANALYTE	%	TIME	AREA
HbF	22.2	1.18	313555
HbS	2.3	1.69	29191
HbA	23.0	2.62	287306
HbA_2	4.4	3.69	55665
Unknown	46.7	4.50	582603
	TOTAL AREA		1268320

F 22.2% A2 4.4%

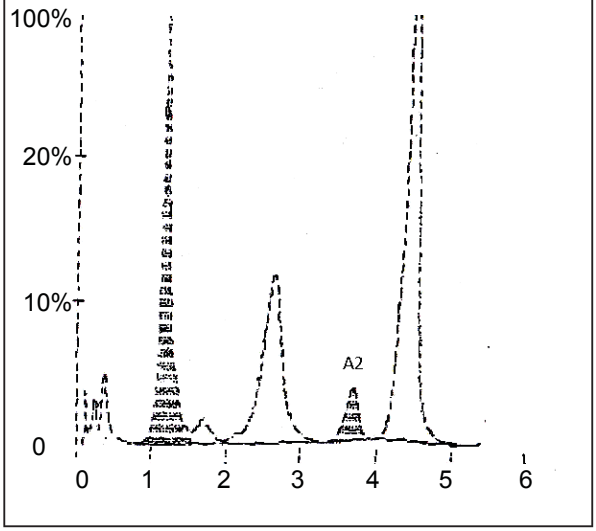

Fig 1: Showing HPLC report of the patient.

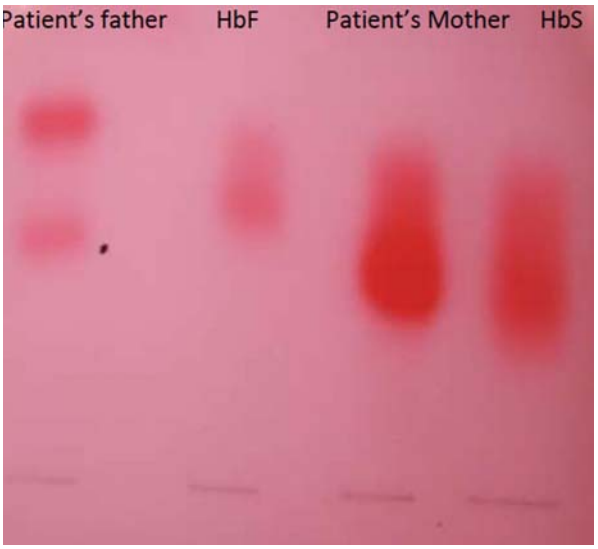

Fig 2: Showing Hb electrophoresis report of the parents

Complete hematological profile and peripheral blood picture of the patient's mother was within normal limits. Sickling test was positive in 30% of cells. Hb electrophoresis revealed a band at SD region. HPLC showed HbF-3%, HbA-56.7%, HbA2-3.9% and HbS-34%. The mother was thus proved to be a case of sickle cell trait.

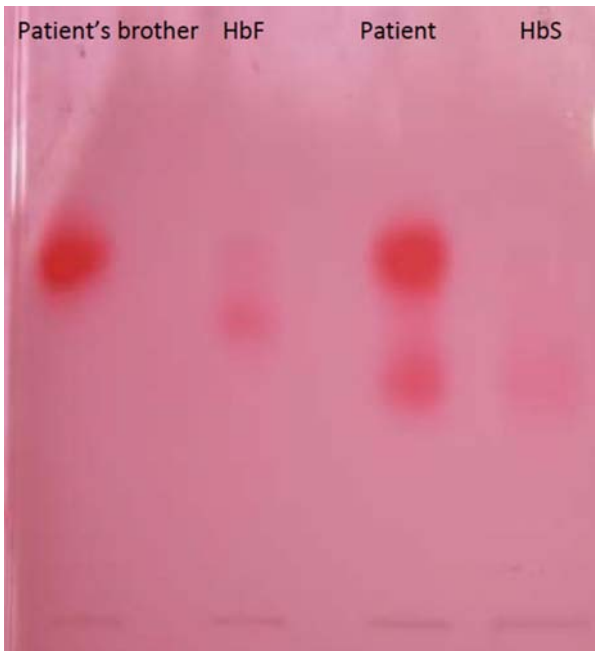

Fig 3: Hb electrophoresis report of the patient and his brother.

Complete blood picture of the patient's younger brother revealed Hb-10.3 gm%, MCV-58.8 fl, TRBCs-5.19x10^6/µL, Mentzer's index-11.3 with microcytic hypochromic cells with mild anisopoikilocytosis. Sickling test was negative. Hb electrophoresis showed F band in F region. HPLC showed HbF-1.3%, HbA-53.2%, HbA2-3.6% and unknown-35.5%. His brother was thus diagnosed as a case of beta thalassemia trait.

The patient's complete blood picture showed Hb-8.4 gm%, MCV-72.5 fl, TRBC-3.38x10^6/uL with microcytic hypochromic red cells with target cells and anisocytosis. Sickling test was positive in very few red cells. Hb electrophoresis showed S and F band on SD and F region respectively. HPLC (Fig 1) showed HbF-22.2%, HbA-23%, HbA2-4.4% and unknown band-46.7%. Hb electrophoresis of the entire family is shown in the Figures 2 and 3.

Considering the complete family picture, the patient was thus diagnosed as double heterozygous sickle cell and thalassemia trait. The parents were counseled regarding the disease and future precautions, especially the genetic aspects. Immunization against the encapsulated organisms was done. He was started on treatment with hydroxyurea. He is presently asymptomatic and is on regular follow up.

Discussion

Hemoglobin S (HbS) is the result of a single base pair change, thymine for adenine, at the 6th codon of the β-globin gene which encodes valine instead of glutamine in the 6th position in the β-globin molecule. Sickle cell anemia occurs when both β-globin genes have the sickle cell mutation resulting homozygous HbSS. When one β-globin gene mutation includes the sickle cell mutation and the 2nd β-globin includes a gene mutation in the β-globin gene other than the sickle cell mutation, such as mutations associated with HbC, Hb β-thalassemia, HbD, and HbO Arab, it results in spectrum of sickle cell disease (SCD)[1].

SCD is one of the most common genetic diseases worldwide with variable distribution, being extremely prevalent in sub-Saharan Africa and India, as a consequence of protection against falciparum malaria afforded by sickle cell trait[2].

The basic pathophysiology in sickle cell disease includes sickling and vasoocclusion. Red cells possessing HbS become insoluble or rigid when passing through spleen, liver, kidneys, joints, and extremities, because of low oxygen concentration. They form liquid tactoids or polymers of hemoglobin and become irreversibly sickled. They obstruct small vessels and adhere to vascular endothelium, increasing the viscosity of the blood as circulation is slowed. This deprives the tissue of oxygen, reducing blood pH, escalating the sickling process further and leading to sickling crisis. The microvascular occlusion leads to tissue ischemia and infarction and ultimately chronic organ failure[3].

In sickle cell disease, clinical manifestations become apparent only after the first 6– 9 months of age because high levels of HbF inhibit sickling before that age. The first clinical manifestation is often sickle cell dactylitis. Other acute presentations include infections, acute chest syndromes, acute pain syndromes, splenic sequestrations, vasocclusive crisis, aplastic crisis, stroke, priapism, bone infarction, nephropathy etc. Chronic features include poor and delayed growth, functional asplenia, cholelithiasis, chronic organ damage etc[4]. The variability in the spectrum of sickle cell disease, extending from almost a normal child to a child with chronic intractable problems, presents great challenges to the treating physician[2].

HbF is the predominant hemoglobin at birth, comprising about 80% of all detectable hemoglobins. HbA usually comprises 20% and HbA2 is normally not detectable to any major extent. By 6 months of age, HbA becomes the major hemoglobin and HbF falls to about 5–10%, while HbA2 has reached adult levels. Individuals with HbSS, HbSC, HbS/alpha-thalassemia do not produce HbA. Individuals with HbS/beta-thalassemia produce some HbA, usually 3–20%. HbA2 is elevated in those with an associated alpha or thalassemia. HbF may continue to be present at higher than expected levels in those with HbSS[5]. In sickle cell anemia, HbS is commonly as high as 90% of the total hemoglobin. In sickle cell disease, HbS is >50% of all hemoglobin[1].

Concomitant presence of various traits like thalassaemia causes reduction in the intracellular concentration of HbS, resulting in less sickling and hemolysis and higher Hb level[6,7]. Hence, coinheritance of disorders with hereditary persistence of fetal hemoglobin, iron deficiency anemia, alpha thalassemic traits etc can modify the spectrum in sickle cell disease[5].

Laboratory investigations in sickle cell disease will show anemia and reticulocytosis. Blood film may show anisopoikilocytosis with increased polychromasia, target cells and sickle cells. H-J bodies may be present by 1 year of age, which represents hyposplenism. Evidence of hemolysis may be present in the form of increased LDH and bilirubin levels and decreased haptoglobin levels. Sickle solubility test detects the presence of HbS, where the blood is mixed with deoxygenating substance to look for resulting turbidity. Definitive diagnosis is hemoglobin identification, which can be done by hemoglobin electrophoresis, high paper liquid chromatography, isoelectric focusing, mass spectrometry or DNA testing[5].

The management should include the immediate treatment of acute complications, detailed counseling including the education and psychosocial support, and genetic counseling if required, maintenance therapy and definitive therapy[4].

Acute management of painful vaso-occlusive episodes includes adequate hydration and analgesia including opoids[1]. Supplemental oxygen, correction of acidosis, aggressive treatment of associated infections all play key role in acute management of vaso-occlusive crisis. Hemoglobin level should be kept optimum to prevent vasocclusion and maintain oxygenation. Transfusions are indicated only during acute severe exacerbations of anemia, as during splenic crisis or aplastic crisis. Prophylactic penicillin prophylaxis is used till 5 years of age. Immunizations against the encapsulated organisms are of priority[4]. Hydroxyurea, a myelosuppressive agent, is a prototype drug which

increases fetal hemoglobin, reduces episodes of vaso-occlusive pain, acute chest syndrome and the need for blood transfusions and helps in prevention of chronic organ damage, leading to improved survival[8-10]. Definitive therapy includes stem cell transplantation[4]. Gene therapy is the new modality of treatment which is still in nascent phase.

Conclusion

Haemoglobinopathies can represent a diagnostic challenge to any physician. Correct diagnosis at the earliest would go a long way in improving the prognosis as well as enhancing the quality of life in such patients. For this, the working knowledge of the basics of haemoglobninaopathies and disease mechanism is fundamental. The importance of regular follow up, treatment, education, genetic counseling and energetic management of complications cannot be over emphasized in such cases.

Informed written consent was taken from the patient parents for the publication.

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