JK SCIENCE pISSN: 0972-1177

CASE REPORT

A Rare Hemoglobinopathy Presenting as Chronic Hyperbilirubinemia

Lenaa Sakthiyavathy Manivannan, Kanimozhi Thandapani, Arulkumaran Arunagirinathan

Abstract

Sickle beta thalassemia represents the double heterozygous state of HbS and beta-thalassemia genes. Clinical manifestation varies from those indistinguishable from homozygous sickle cell anemia to completely asymptomatic ones. This disorder is diagnosed by increased levels of HbS, HbF, mildly increased HbA2 and varying levels of HbA on Hemoglobin electrophoresis. We report a 13 yrs. old girl who presented to us with jaundice for one year with hepatosplenomegaly and no history of blood transfusions or sickle cell crisis. Hb electrophoresis clinched the diagnosis of sickle beta thalassemia.

Key Words

Sickle beta thalassemia, Hb electrophoresis, HbS, HbF, HbA

Introduction

Sickle beta thalassemia is a disorder which represents the double heterozygous state for the HbS and the beta thalassemia genes. It is a rare hemoglobinopathy with a prevalence of less than 1% in India (1,2).

Case Report

A 13-year girl, fourth order child born of non-consanguineous marriage from south India, presented with complaints of yellowish discolouration of eyes for one year which is not progressive. Child passes normal colour urine and stools. No history of fever/hematemesis/altered sleep cycle/blood transfusion or similar complaints in the past. No family history of blood transfusion/chronic liver disease. No prior hospitalisation.

On examination, she was conscious, oriented with pallor and icterus. No lymphadenopathy/ edema. Abdominal examination revealed hepatomegaly with liver span 6cm and splenomegaly which was firm 2 cm below left costal margin. Other system examinations were unremarkable.

Her complete blood count revealed anemia (Hb 8.8 g%), RBCs 4.5 million/cumm, MCV 77.3 fL, MCH 19.4 pg, with normal total count and platelet count. Peripheral smear showed microcytic, hypochromic red cells, with few target cells, tear drop cells, bite cells, spherocytes, polychromatic cells, schistocytes - microcytic, hypochromic anemia with features of hemolytic anemia. Reticulocyte count was elevated (7%). Serum ferritin was 123.9 ng/mL (normal). G6PD levels were normal. Osmotic fragility was decreased which was suggestive of thalassemia.

Her biochemical parameters showed mild hemolysis with total bilirubin 4.4 mg/dL (direct bilirubin 0.4 mg/dL), Lactate dehydrogenase (LDH) – 526 IU. Liver enzymes, serum albumin and PT/INR were normal. Direct coomb's test was negative. Urine bile salts/ bile pigments absent.

Department of Pediatrics, Sri Manakula Vinayagar Medical College and Hospital, Madagadipet, Pondicherry, India

Correspondence to: Dr. Lenaa Sakthiyavathy M, No. 9, First Cross, SBI Colony (Near Rajiv Gandhi Women and Children Hospital), Pondicherry- 605005, India

Manuscript Received: 24 August 2020; **Revision Accepted**: 15 November 2020; **Published Online First**: 20 August 2021

Open Access at: https://journal.jkscience.org

Cite this article as: Manivannan LS, Thandapani K, Arunagirinathan A. A rare hemoglobinopathy presenting as chronic hyperbilirubinemia. JK Science 2021;23(3):162-164.

HBsAg, anti-HCV negative. Ophthalmology opinion sought - no evidence of Kayser-Fleischer ring. Hb Electrophoresis revealed HbS 64.2%, HbA2 4.2%, Hb F 31.6% suggestive of sickle beta thalassemia (*Figure 1*). Child was started on tab Folic acid/Hydroxyurea and was advised regular follow up.

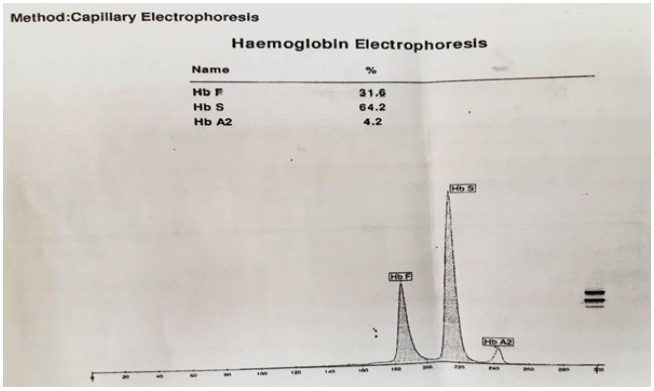

Figure 1. Hb Electrophoresis Report Showing Elevated HbS and HbF with Absent HbA1

Discussion

Sickle cell disease refers to homozygous HbSS and also to all genotypes in which HbS interacts with other globin gene mutations. The clinical course of these phenotypes is extremely variable. Sickling symptoms if present, are often milder than those noted in patients with homozygous sickle cell anemia.

HbS/ Beta thalassemia is clinically more similar to sickle cell disease than to thalassemia major or intermedia. Those who inherit a β0 gene are clinically indistinguishable from those with homozygous sickle cell anemia and have very low levels of HbA. Those with β+ genes present milder phenotypes and may be asymptomatic because of the higher levels of HbA.

Sickle cell disease is characterized by intermittent vaso-occlusive events and chronic hemolytic anemia. Clinical manifestations include sickle cell dactylitis, infections, acute chest syndromes, acute pain syndromes, splenic sequestrations, vaso-occlusive crisis, aplastic crisis, stroke, priapism, bone infarction, nephropathy. Chronic features include poor and delayed growth, functional asplenia, cholelithiasis.

HbS/Beta thalassemia presents with higher RBC counts and HbA2 levels and lower MCV and MCH values (mean 68 fL and 20 pg respectively) compared to HbSS. Splenomegaly is more common in patients with HbS/Beta thalassemia, compared to HbSS, and the spleen tends to remain enlarged and functional in adulthood (3).

In HbS/ Beta thalassemia, HbS is the most abundant Hb, HbA2 is increased, and HbF may be normal or variably increased. HbA is < 30% with β+ gene mutations whereas HbA is absent in β0 mutations (3).

Our child presented with chronic hyperbilirubinemia and hepatosplenomegaly raising the suspicion of chronic liver disease and hemolytic anemia. Her Liver function test including PT/INR was normal. HBsAg and anti HCV were negative. Since reticulocyte count was elevated and peripheral smear was suggestive of hemolytic anemia, she was worked up for the same and Hb electrophoresis was done which was suggestive of sickle beta thalassemia.

Acute management of painful vaso-occlusive episodes include adequate hydration and analgesia including opioids. Supplemental oxygen, correction of acidosis, aggressive treatment of associated infections. Hemoglobin level should be optimum to prevent vaso-occlusion and maintain oxygenation. Transfusions are indicated only during acute severe anemia, as during splenic crisis or aplastic crisis. Prophylactic penicillin is used till five years of age. Immunization against the encapsulated organisms is 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 (5).

Definitive therapy includes stem cell transplantation from a healthy donor or one with sickle cell trait (4). Children with sickle cell disease receiving stem cell transplantation using a matched sibling donor can expect a 92% chance of cure with an overall survival of 95% (6). Gene therapy is the newer modality of treatment which is still in nascent phase (7). Gene editing and gene addition approaches are being pursued, but only viral mediated gene therapy approaches are being used in clinical trials (8,9). The use of selectin antagonists like Crizanlizumab and Rivapanzel is currently under clinical trials. These agents reduce vaso-occlusive damage through actions on red blood cell and endothelial receptors (10).

Conclusion

Sickle beta thalassemia is of two types - one characterized by complete absence of HbA due to presence of a β0 thalassemia gene with a more severe disease course than the other with HbA levels of 10 to

30% due to a β+ gene. Hemoglobinopathies are common. Sickle beta thalassemia being a rare variant can prove fatal but newer treatment options have improved the quality of life and life span in people with sickle beta thalassemia.

Financial Support and Sponsorship
Nil.

Conflicts of Interest
There are no conflicts of interest.

References

1. Balgir RS. Spectrum of hemoglobinopathies in the state of Orissa, India: a ten years cohort study. *J Assoc Physicians India* 2005;53:1021-26.
2. Mohanty D, Colah RB, Gorakshakar AC, Patel RZ, Master DC, Mahanta J, *et al.* Prevalence of β-thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. *J Community Genet* 2013;4(1):33-42.
3. Hankins JS, Wang WC. Sickle cell anemia and other sickling syndromes. In: Greer JP, Arber DA, Glader B, List AF, Means RT, Paraskevas F, *et al.* editors. *Wintrobe's Clinical Hematology.* 13th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins Health; 2014. p. 823-59.
4. Daniel RA. Hematologic disorders. In: Hay WW, Levin MJ, Sondheimer JM, Deterding RR, editors. *Current Pediatrics.* 20th ed. New York: McGraw Hill Companies; 2010. p. 845-49.
5. de Montalembert M, Brousse V, Elie C, Bernaudin F, Shi J, Landais P, *et al.* Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes. *Haematologica* 2006;91(1):125-28.
6. King A, Shenoy S. Evidence-based focused review of the status of hematopoietic stem cell transplantation as treatment of sickle cell disease and thalassemia. *Blood* 2014;123(20):3089-94.
7. Bender MA. Sickle Cell Disease. 2003 Sep 15 [Updated 2017 Aug 17]. In: Adam MP, Ardinger HH, Pagon RA, *et al.*, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
8. Ikawa Y, Miccio A, Magrin E, Kwiatkowski JL, Rivella S, Cavazzana M. Gene therapy of hemoglobinopathies: progress and future challenges. *Hum Mol Genet* 2019;28(R1):R24-30.
9. Goodman MA, Malik P. The potential of gene therapy approaches for the treatment of hemoglobinopathies: achievements and challenges. *Ther Adv Hematol* 2016;7(5):302-15.
10. Schamess A, Desai P. Primary care of patients with sickle cell disease. *J Gen Med Prim Care* 2017;1(1):100006.