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Compound Heterozygous Sickle Cell – β$^-$ Thalassemia: Diagnosed After Family Study By HPLC In A Patient Presenting With Acute Chest Pain, Fever, Jaundice And Weakness

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Abstract

Sickle cell β thalassemia (HbS/β$^-$ thallasemia) results from the combination of sickle cell mutation and β thalassemia mutation. Presence of traits like thalassemia, persistence of fetal hemoglobin, presence of HbE and Hb D can modify the spectrum in sickle cell disease. We report a case of 28 year old male who presented with generalized weakness, bone pains and fever on and off. On investigations of patient and family members, he turned out to be a case of compound heterozygous sickle cell and thalassemia trait subsequently. The patient was given blood transfusion and was counseled for treatment with hydroxyurea. Thus, family testing is of utmost importance as falsely elevated HbA_2 in SCD may be due to transfusion and may lead to incorrect diagnosis of heterozygous sickle cell thalassemia trait. Confirmation requires genetic testing which shows sickle cell mutation and globin chain mutations.

Keywords: Family testing, genetic testing, hydroxyurea, sickle cell, thalassemia

Introduction

Sickle cell disease and thalassemia are two most common forms of hemoglobinopathies in India [1]. Sickle cell β thalassemia (HbS/β$^-$ thallasemia) results from the combination of sickle cell mutation and β thalassemia mutation. β thalassemia is more prevalent in Mediterranean countries, the Middle east, Central Asia, India, North coast of Africa and South America. The prevalence of sickle cell disorders in India is 4.3%, but, the association of β thalassemia with sickle cell anemia is rare which is reported to be just 1.7% [2]. Presence of traits like thalassemia, persistence of fetal hemoglobin, presence of HbE and Hb D can modify the spectrum in sickle cell disease. Presence of HbF inhibits sickling and thus may reduce hemolysis and symptoms associated with sickle cell disease [3]. We report a case of 28 year old male who presented with generalized weakness, bone pains and fever on and off. On investigations of patient and family members, he turned out to be a case of compound heterozygous sickle cell and thalassemia trait subsequently.

Case Report

A 28 year old male was admitted with history of generalized weakness, low grade fever, loss of apetite, on and off chest pain and yellowish discoloration of eyes. There was history of covid vaccination 7 days back. Past history of multiple episodes of weakness, mild jaundice and fever along with a documented history of low Hb levels since childhood with serial investigations and prescriptions for similar complaints in the past was present. General examination revealed pallor and mild icterus. BP was 150/80mm Hg. On systemic examination, liver was palpable 3 cm below right subcostal angle and spleen was not palpable. Rest of systemic examination was within normal limits. Laboratory

investigations revealed Hb- 5.5gm/dl, MCV-70fl, RBC count- $2.18x10^6$/cmm. Blood picture was microcytic hypochromic with mild anisopoikilocytosis, target cells and few sickle cells (Figure 1). During indoor stay, blood picture did not respond to conventional iron supplementation. HPLC revealed HbF-17.9%, HbA_2-4.8%, HbA-3.7% and HbS – 68.5% (Figure 2). Sickling test was positive. Thus provisional diagnosis of double heterozygous sickle cell and thalassemia trait was made. Subsequently, complete blood count and HPLC of patient's mother, father, brother and son was done after due counseling and informed consent. Complete blood count of mother revealed Hb- 11.7 gm/dl, MCV-73fl and RBC count-$4.83x10^6$/cmm and HPLC revealed HbF<0.8%, HbA_2-3.2%, HbA-51.4% and HbS- 34.8%, (Figure 3). Thus, she was diagnosed as a case of sickle cell trait. Complete blood count of father showed Hb- 10.3g/dl, MCV- 77.8fl and RBC count -$4.40x10^6$/cmm. HPLC showed HbF-1.8%, Hb A_2- 4.2%, HbA- and HbS- 0% which was consistent with beta thallasemia trait/minor (Figure 4). Thus, the patient's diagnosis of heterozygous state for β thallasemia sickle cell trait was confirmed. CBC and HPLC of brother was normal. CBC of son of patient who was 2 year old revealed Hb- 11.0g/dl, MCV-68.9fl, and RBC count- $4.99x10^6$/cmm and HPLC showed HbF- 1.9%, HbA_2- 2.7%, HbA- 58% and HbS- 30.8% which was consistent with sickle cell trait. Sickling test was positive. Genetic counseling of the patient and his wife was done for future precautions in view of family planning. He was given blood transfusion and was counseled for treatment with hydroxyurea. Patient and his son are presently asymptomatic and on regular follow up.

Figure1: PBF of patient showing sickle cell (arrow) and target cells

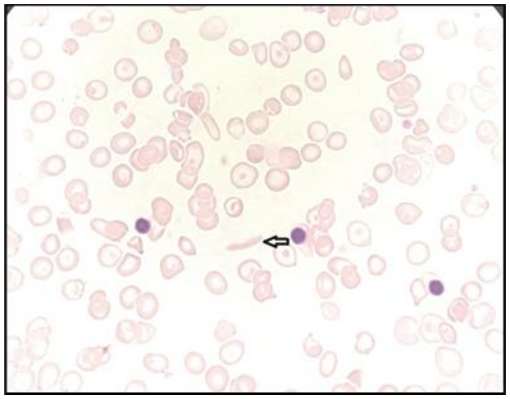
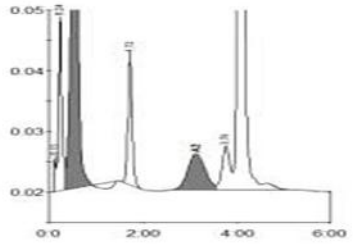


Figure2: HPLC report of patient



Peak table -

Peak	R.time	Height	Area	Area %
Unknown	0.13	5727	12976	0.4
A1a	0.24	28569	140163	4.0
F	0.55	60918	590561	17.9 *
A0	1.72	22104	129846	3.7
A2	3.12	5898	151323	4.8
Unknown	3.76	7192	83380	2.4
S-Window	4.05	333025	2412979	68.5
Total Area:		3521227		

Concentration:	%
F	17.9 *
A2	4.8

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Figure 3: HPLC report of patient's mother

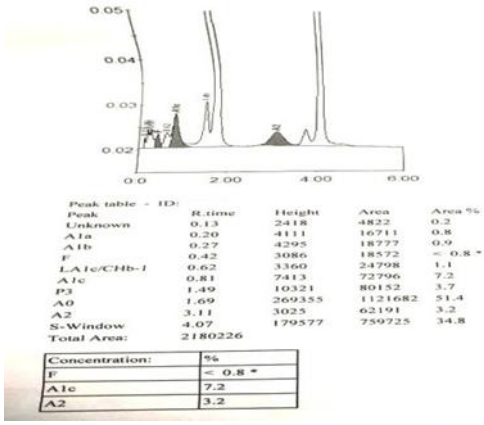
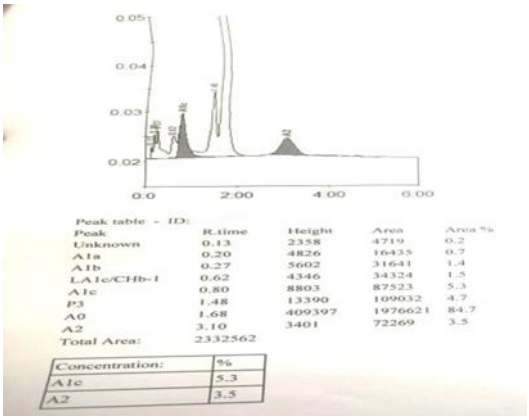


Figure 4: HPLC report of patient's father



Discussion

Sickle cell disease is an autosomal recessive hemolytic anemia with presence of HbS, which results from substitution of hydrophilic glutamic acid with hydrophobic valine in position 6 of beta globin gene [4]. Red cells possessing HbS become insoluble or rigid when exposed to low oxygen concentration especially while passing through spleen, liver, kidneys, joints and extremities. The RBCs undergo repeated cycles of sickling that result in vaso-occlusive pain crisis. RBC lifespan is reduced to upto 1/6 th of normal RBCs[5,6]. The inheritance of HbS or alpha globin gene mutation variants results in several SCD subtyped including Sickle cell SS (sickle cell anemia), SC (sickle cell trait), $S\beta^0$ and $S\beta^+$. SC and $S\beta^+$ are rarer subtypes resulting in less severe anaemia and infrequent vaso-occlusive crisis in childhood as in our case. These rarer subtypes may gradually develop acute complications including acute chest syndrome, vaso occlusive crisis, splenic sequestration, aplastic crisis, stroke, priapism, bone infarctions etc. chronic manifestations include asplenia due to autosplenectomy, poor and delayed growth, cholelithiasis, chronic organ damage etc [7-9]. Patients with HbS/β thalassemia can be divided into two categories on the basis of presence of Hb A(HbS/β^+ thalassemia) and absence of HbA (HbS/β^0 thalassemia). Presence of HbA in HbS/β^{-+} thalassemia dilutes the Hb S levels and its effects and inhibits Hb polymerization induced cellular damage to some extent and such patients may not develop symptoms until onset of puberty or early adult life. Patients with HbS/β^0 thalassemia have lower Hb levels and more rapid hemolysis[10,11].

The patient's mother and son were diagnosed as sickle cell traits which are also relatively rare

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conditions. Family testing of the patient confirmed the co-inheritance of sickle cell mutation with globin chain mutation in which HPLC findings of mother were consistent with sickle cell tarit and of father were consistent with β thalassemia trait. Family testing is of utmost importance as falsely elevated HbA_2 in SCD may be due to transfusion and may lead to incorrect diagnosis of heterozygous sickle cell thalassemia trait. Confirmation requires genetic testing which shows sickle cell mutation and globin chain mutations [12,13]. So, presence of hypochromic microcytosis in individual with sickle cell disease in absence of iron deficiency should always raise suspicion of additional alpha or beta globin chain abnormalities.

Management of patient includes treatment of acute complications, genetic counseling including education and psychosocial support, maintenance therapy. Acute management of painful vaso-occlusive episodes includes fluid supplements, aggressive use of appropriate analgesics, broad spectrum antibiotics along with oxygen therapy. Blood transfusion can be given with persistent hypoxia. The most promising antisickling agent is hydroxyurea which has the ability to induce fetal hemoglobin synthesis. It decreases the number of vaso-occlusive episodes and painful crises, helps preserve organ function and increases life span. The drug is contraindicated during pregnancy. Co-administration of other hematopoietic agents such as butyric acid or erythropoietin may also be helpful. Penicillin prophylaxis is recommended to prevent infection and sickle cell crises. Bone marrow transplantation has a cure rate of 70-80% although only 35% patients would have immunologically competent donors. Gene therapy is still at an experimental stage. Pre-natal diagnosis by chorionic villous sampling is possible but it does not predict severity of disease[14-16].

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