RESEARCH PAPER | Medical Science | Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

Sickle β thalassaemia with hypersplenism & crisis, a rare occurrence

KEYWORDS: sickle cell anemia, thalassaemia, hypersplenism

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ABSTRACT *Sickle β thalassaemia is a heterogeneous disorder with a variable clinical expression ranging from a symptomless state to a condition indistinguishable from homozygous sickle cell anemia. Sickle β thalassaemia is generally thought to represent the milder end of the spectrum of sickle cell syndromes. We describe a case 13 years/female having sickle β thalassaemia with hypersplenism who also had crisis illustrating that sickle β thalassaemia may run an unexpected clinical course. Sickle β thalassaemia is due to the interaction between HbS and the mild form of β thalassaemia which has an inhibitory effect on red cell sickling due to HbA.1 However, it is important to emphasize that serious complications may occur unexpectedly as is shown by our patient. This makes the case important to report.*

Introduction:
Sickle β thalassaemia represents the double heterozygous state for the HbS and the β thalassaemia genes. Sickle β thalassaemia is a relatively rare disorder. It is sometimes characterised by an early onset, marked anemia and a high mortality rate in childhood, painful crises, hepatosplenomegaly and other complications. Some patients who are less severely affected reach adult life without major symptoms. The late persistence of splenomegaly in these patients predisposes them to increased morbidity.

Case:
A 13 years/female admitted with the complains of generalized weakness, easy fatigability since childhood. Patient also complained of painless slowly growing swelling in left side of abdomen. There was H/O poor weight gain since childhood. Patient's mother told us about 3 events of hospitalization at local hospital in the past, characterized by shortness of breath, fever & pain in abdomen. She had suffered from recurrent jaundice in childhood. No history of abnormal bleeding tendency. No history of blood transfusion in the past. Birth history was not contributing and parents were apparently healthy. On examination , patient was malnourished (height 133cm, weight 28 kg, BMI 15.8 kg/m^2), pale and icteric. No lymphadenopathy or bony tenderness was present. No obvious skeletal dysmorphic features were noted. Mild hepatomegaly and gross non tender splenomegaly was present. No evidence of free fluid in abdomen. Soft systolic murmur was heard at apex. Lung bases were clear. No other remarkable findings were noted. From these symptoms & signs we suspected haemolytic anemia. Investigation results were as follows. Haemoglobin 4.7gm%, TLC 4000/cmm, platelets 75000/cmm. Peripheral smear was suggestive of microcytosis with hypochromia, some degree of anisopoikilocytosis with pencil cells and target cells. Retic count 3.2%. Serum LDH- increased (843 IU/L). Renal functions were normal. Liver Function Tests showed indirect hyperbilirubinemia with normal liver enzymes. Serum Albumin was normal. PT- 17.2 seconds (control-13 seconds). USG abdomen was suggestive of mildly enlarged liver, normal portal vein diameter, severe splenomegaly with ill defined hypo echoic areas at upper pole of spleen most likely splenic infarcts & no evidence of free fluid. Serum Iron and TIBC were within normal limits. Direct Coomb's test was negative and Sickling was positive. Father's Sickling test was positive and Mother's negative. Though sickling test was positive but in view of huge splenomegaly, we thought of some other haemoglobinopathy associated like thalassaemia. Hence Hb electrophoresis was also asked. During her hospital stay, patient was being treated conservatively. Suddenly one day, she developed severe dyspnoea with pain in abdomen & drop in Hb which probably correspond to sickle cell crisis. Patient improved with the oxygenation and hydration in few days time. At this point, we recall about similar episodes in the past being treated at local hospital. Hb electrophoresis revealed following pattern:

Table I: Hb Electrophoresis report

Hb subtype	Observed value (%)	Normal range in adults
HbF	28.6	Upto 1%
HbA	1.6	96.8 to 97.8%
HbA2	4.7	1.8 to 3.5 %
HbS	63.7	_

From above findings, it is clear that patient was suffering from sickle β thalassaemia. Gross splenomegaly with low counts suggested presence of associated hypersplenism. Patient was started on hydroxyurea therapy & sent for splenectomy.

Discussion:
Hemoglobinopathies are autosomal co-dominant traits—compound heterozygotes who inherit a different abnormal mutant allele from each parent exhibit composite features of each. Like, patients inheriting sickle β thalassemia exhibit features of thalassemia and sickle cell anemia.[2,3] Thalassemias are the most common genetic disorders in the world, affecting nearly 200 million people worldwide. Sickle cell disease is the most common structural haemoglobinopathy occurring in heterozygous form. Sickle cell disease displays a unique progression in certain parts of the world like Eastern province of Saudi Arabia, where splenomegaly with hypersplenism is noted with high frequency in the adolescent and adult patients. The late persistence of splenomegaly although likely reflects the milder progression of sickle cell disease in this region; nevertheless, it predisposes the patients to increased morbidity. Multiple responsible factors have been evaluated to explain this progression, the most widely accepted being the occurrence of Asian haplotype of β^S globin gene, high levels of fetal haemoglobin (HbF), and frequent β -thalassemia. The enlarged spleen causes further morbidity by predisposing the patient to the complications of acute splenic sequestration crises, chronic hypersplenism,

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

infarction, and abscess formation. The defective function of the enlarged spleen is another concern for the patient's management because the spleen may not be able to protect the patient from recurrent infections, thus further contributing in the morbidity associated with sickle cell disease in this region. Late, persistent splenomegaly has also been reported in the 5%of Jamaican (similar to North America), 19% of Greek, and 69% of Indian sickle cell disease patient populations. In the former two population groups, the predominant β^S globin gene haplotype is of Benin type. It is characterized by a high frequency of vascular occlusive crises, nephropathy, priapism, stroke, infections, major-type acute splenic sequestration crises, and early autosplenectomy . [4,5]Indian sickle cell disease has been found similar to that occurring in eastern Saudi Arabia and shares the same Asian haplotype of the β^S globin gene , and has been reported to be of mild nature with lower incidences of stroke, priapism, nephropathy, fewer vasoocclusive crises, late splenomegaly persistence, late and variable functional asplenia, and lower mortality.[4,5] Clinical and haematological features have been summarized in table II.

Table II: Clinical features of sickle haemoglobinopathies:[2,3]

Condition	Clinical Features	Hb level (g/dl)	Hb electrophoresis
Sickle cell trait	None; rare painless hematuria	Normal	Hb S/A:40/60
Sickle cell anemia	Vasoocclusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers	7–10	Hb S/A:100/0 Hb F:2–25%
S/ β^0 thalassemia	Vasoocclusive crises; aseptic necrosis of bone	7–10	Hb S/A:100/0 Hb F:1–10%
S/ β^+ thalassemia	Rare crises and aseptic necrosis	10–14	Hb S/A:60/40
Hemoglobin SC	Rare crises and aseptic necrosis; painless hematuria	10–14	Hb S/A:50/0 Hb C:50%

Blood picture in sickle β thalassaemia is similar to that of β thalassaemia major. The haemoglobin level in β^0 thalassaemia is low, usually 6 to 9 gram %. In β^+ type, it is 10 to 11 gram%. Microcytosis, marked hypochromia, and target cells are the main features in the blood film. A small number of sickle cells are often seen. The MCV and MCH are greatly reduced, the reticulocyte count is mildly elevated. The haemoglobin pattern of the β^0 type consists almost totally of Hb-S with a mild increase in Hb-F and Hb-A_2 .[3,6] There is no Hb-A. The β^+ type consists of Hb-S, Hb-A 10 to 30%, mild increase in Hb-F and Hb-A_2. Cases with very small amount of Hb-A may be diagnosed as homozygous sickle cell disease, the Hb-A being visually lost in increased Hb-F. Examination of other family members, genetic studies, & globin chain synthesis studies are helpful in doubtful cases. Antenatal diagnosis of thalassemia syndromes is now widely available.[2,3,5]

The diagnosis of S-thalassaemia in above described case was made by the presence of HbS as the major hemoglobin component in association with the following : (1) elevation of HbA2, greater than 2.5%; (2) presence of HbA without transfusion history ; (3) abnormal red cell morphology with hypochromic, microcytic cells, and many target cells; (4) splenomegaly; & (5) family history compatible with the diagnosis.[7]

Complications:
Anaemia, vasoocclusive crisis and leg ulcers, gallstones, bone necrosis, stroke & iron overload etc. Splenic complications are: acute splenic sequestration, splenic abscess, infarction & hypersplenism.

Treatment:
Many patients require chronic transfusion therapy designed to maintain a hematocrit of at least 27–30% so that erythropoiesis is suppressed. Folic acid supplements may be useful. Vaccination in anticipation of eventual splenectomy is advised. Chronic blood transfusion can lead to blood borne infections, alloimmunization, febrile reactions, and lethal iron overload. Hence iron chelating agent should be considered at appropriate step. Acute crisis & other complications should be anticipated & treated promptly. Reestablishing high levels of fetal hemoglobin synthesis should ameliorate the symptoms. Cytotoxic agents such as hydroxyurea promote high levels of HbF synthesis.[2,3,8] Bone marrow transplantation provides stem cells able to express normal hemoglobin; it has been used in a large number of patients with β thalassemia and a smaller number of patients with sickle cell anemia.

Role of splenectomy:
Because of diversity of presentation, regional variations, & probably due to fewer crisis episodes & higher level of HbF; splenomegaly is found in some adult patients of sickle β thalassemia. Patients do suffer from splenomegaly because of extramedullary haematopoiesis, increased RBC destruction, repeated blood transfusions and iron overload. Splenectomy is indicated if there is increasing blood transfusion requirement, gross splenomegaly causing hypersplenism or if there are pressure symptoms on surrounding organs. Other indications are acute severe splenic sequestration, splenic abscess, and infarction.[1,5,9,10]

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