

A YOUNG CHILD WITH SICKLE CELL β^0 THALASSEMIA: A CASE REPORT AND REVIEW OF LITERATURES

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Abstract

Recurrent episodes of fever along with bone pain and failure to thrive among children may occur in many clinical situations. Recently, a 28 months old child was admitted in the department of Pediatrics, Dhaka Medical College Hospital with recurrent attacks of fever, severe pain and limitation of movement of both hip joints & cervical spine and who finally diagnosed as sickle cell β^0 Thalassemia. The case is reported here for future references.

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Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder of red blood cells (RBC) in which RBC contain hemoglobin S (Hb-S)¹. The basic problem of Hb-S is that in deoxygenated state RBC become rigid and deformed assuming a sickle or crescent shape (Sickling phenomenon). This in turn decreases cell's flexibility and make the patient risky of various vaso-occlusive complications¹. Hb-S is one of the commonly encountered Hb variants worldwide. In India, its prevalence varies from 0 - 34% in different tribal and some scheduled caste groups but it is seldom reported among children in Bangladesh².

Case Summary

A 28-month-old fully immunized (as per EPI schedule of Bangladesh) boy 2nd issue of his non-consanguineous parents, from a low socio-economic family, was admitted on the 13 December 2011 with high grade continuous fever, pain with restricted movement of both the hip joints and cervical spine for 15 days prior to hospitalization. Pain was so severe that he could not walk. There was neither history of any trauma nor any bleeding associated with the presenting problem. He had similar attack

3 months back, when he was diagnosed as a case of septic arthritis and treated with IV antibiotics and analgesic with some improvement. On further inquiry, his father told that this child had been suffering from recurrent respiratory tract infections and used to remain sick since his 3 months of age and every time he required antibiotic to be cured. His birth history, feeding history were uneventful and no history of such disease in his family. His developmental milestones were age appropriate.

On examination the boy was looking ill, irritable, conscious, lying supine with semi flexed hip and knee joints. He was moderately pale, febrile, temperature was 101°F, Pulse 108/min, Respiratory rate 24 breaths/min, BP 90/50 mmHg, BCG mark was present. His anthropometry revealed, weight 8 kg, height 80 cm and weight for age Z score -4.33SD, height for age Z score -3.2SD (severe stunting), weight for height Z score -3.5SD (severe wasting). There was neither lymphadenopathy nor bony tenderness or bleeding manifestation.

Systemic examination revealed tenderness in both hip joints and cervical spine and had restriction of movement in all modalities. Other

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joints were normal. There was no hepato-splenomegaly. Ophthalmoscopy and other systemic examinations revealed no abnormality.

Laboratory investigations revealed hemoglobin 7.7 gram/dl(anemia), packed cell volume 23.6%, ESR 20 mm in 1st hour, platelet count 9,67,000/cmm(thrombocytosis), total count of WBC 19,240/cmm(leukocytosis), differential count of WBC reveals neutrophil-46.4%, lymphocyte-34.3%, eosinophil-6%, monocyte-



Fig.-1: Our patient with semiflexed lower limb

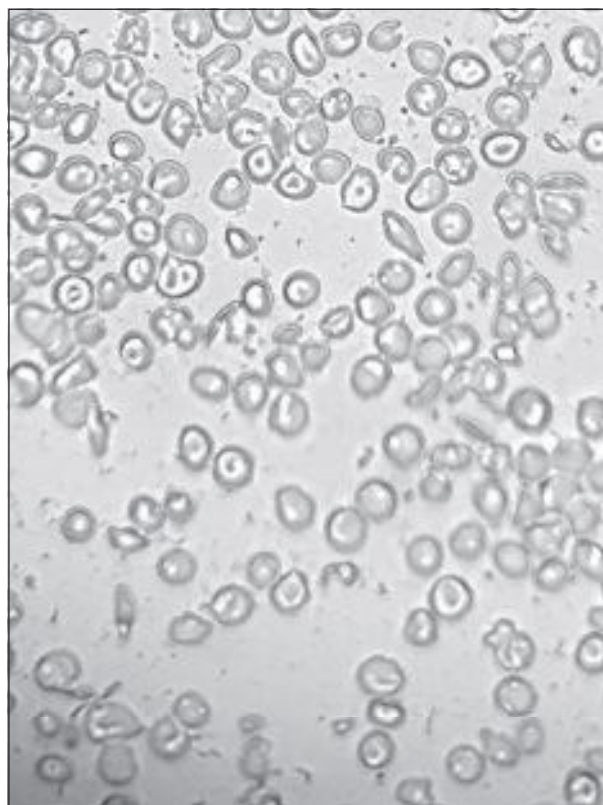


Fig.-2 Sickle shaped RMC

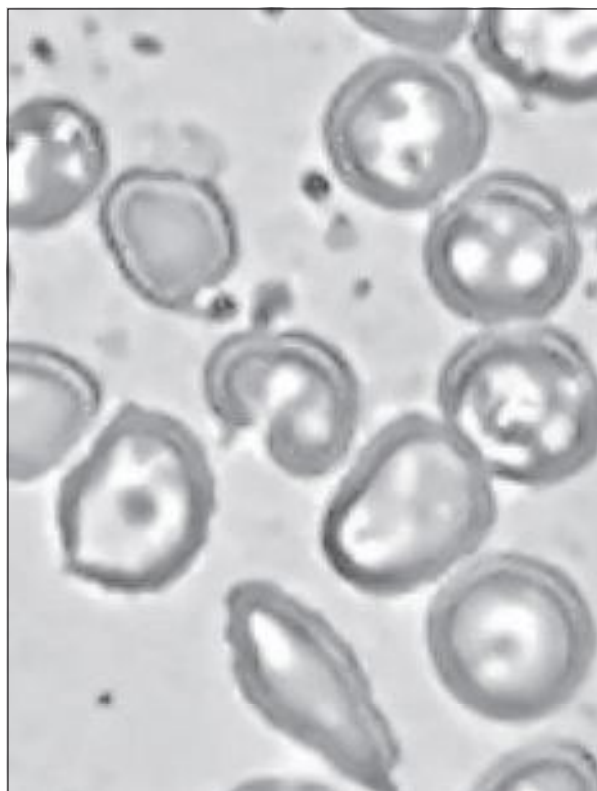


Fig.-3: Target cell and Sickle shaped RBC (magnified)

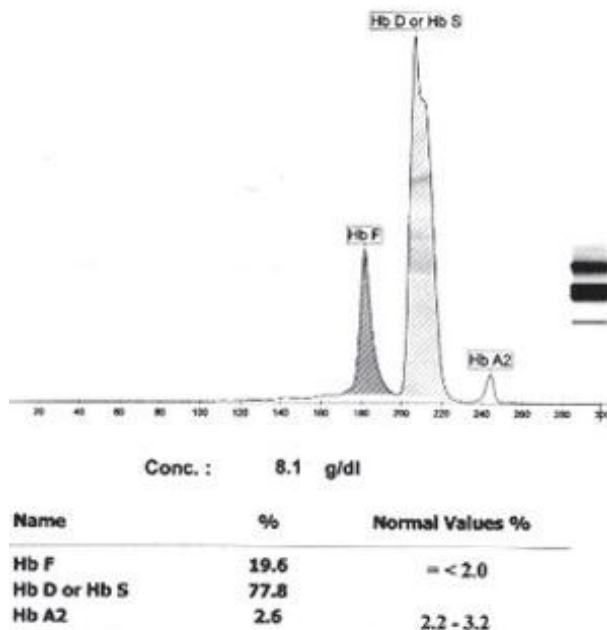


Fig.-4: Hb Electrophoresis of our patient

12.9%, basophil-0.4%. Sepsis screening was normal. Peripheral blood film showed microcytic, hypochromic RBC with anisopoikilocytosis. Few sickle shaped cells and

large number of target cells were also seen on blood film. Sickling test was strongly positive. Hemoglobin capillary electrophoresis showed a broad band in the region of HbS. The quantitative analysis of hemoglobin revealed HbS to be 77.8%, HbF 19.6%, HbA₂ 2.6%. Radiology of chest, long bones and spines as well as ultrasonogram of abdomen was normal. ECG and echocardiography revealed no abnormality. From the above clinical and laboratory findings the case was diagnosed as sickle cell α^0 Thalassemia.

After diagnosis he was managed with Naproxen 10 mg/kg/day in 2 divided doses for 10 days, Ranitidine 3 mg/kg/day in 2 divided doses for 10 days, Penicillin 125 mg bid up to 3 years of his age, Aspirin 10 mg/kg once daily continue up to next follow up, Folic acid 1 mg daily continue up to next follow up. Hydroxyurea 10 mg/kg once daily was also given to the child for next 6 months to review for its efficacy. Eighty ml of packed RBC was transfused to correct his anemia. He was also advised for pneumococcal and meningococcal vaccine.

Discussion

Sickle cell disease (SCD) first described in 1910 is a collective term for a group of blood disorders which includes Sickle cell anemia (Homozygous state, HbS >90%), sickle cell trait (Heterozygous state, HbS <50%) or Compound heterozygous state (HbSC, HbSD, HbSO, HbS α Thalassemia)^{3,4}. Individuals of African descent exhibit the highest frequency of at-risk genotypes associated with Hb-S. However, individuals of Mediterranean, Caribbean, South and Central American, Arab, and East Indian descent also exhibit high frequencies of at-risk genotypes⁵. Among African Americans, approximately 1 in 500 is affected by sickle cell disease, and about 8% has sickle cell trait⁶. The World Health Organization (WHO) estimates that globally 2.3% peoples are carrier of sickle cell disease. Most countries have an uneven distribution of carriers because their populations include different ethnic groups (with different carrier rates, types of hemoglobinopathy and mutations) that have become co-located as a result of migration⁷.

SCD arises from the inheritance of hemoglobin S⁴ resulting from a mutation substituting thymine for adenine in the sixth codon of the beta-chain gene in chromosome 11. This causes coding of valine instead of glutamate in position 6 of the beta chain of hemoglobin¹. The pathological process in sickle cell disease is caused by the sickling phenomenon: in the deoxygenated state, haemoglobin S molecules aggregate into a long polymers which transform the red cell into the characteristic sickle shaped cell and damages the red cell membrane so that it becomes increasingly rigid and is sequestered in the reticuloendothelial system and rapidly destroyed, causing hemolytic anaemia³. A second major disturbance in sickle cell disease arises as a result of altered flow properties of sickled red cells which give rise to increased blood viscosity associated with stasis due to propensity of sickled RBC to adhere to the wall of the small blood vessels and eventually vaso-occlusive crises and permanent organ damage⁸. Furthermore, patients suffering from sickle cell disease have a propensity to bacterial infection owing to a combination of asplenia, defective opsonisation, and other ill defined factors³. Molecular study reveals that next to sickled RBC, endothelial cells and leukocytes play essential role in onset and maintenance of vaso-occlusion in SCD. Endothelial cells when stimulated by cytokines, increase their surface expression of Vascular Cell Adhesion Molecule-1 (VCAM-1), and there by promote sickled RBC and leukocytes adherence and this impedes microcirculation⁸.

Sickle cell disease affects multiple organs of hematological, skeletal, renal, cardio-respiratory, GIT, neurological systems. Cardinal signs include features of hemolytic anemia, painful vaso-occlusive crisis and multiple organ damage from microinfarcts^{9,10,11}. Bone destruction is common in sickle cell disease as a result of painful vaso-occlusive crises as well as in avascular necrosis⁹. In children the only presentation may be chronic low level pain and recurrent infections^{9,12} and our patient presented with fever (without any infective focus), bone pain and failure to thrive. Other clinical manifestations of SCD are delayed sexual maturation, priapism, dactylitis,

acute chest syndrome(ACS), heart failure, cholecystitis, pulmonary hypertension, paraorbital facial infarction and ptosis¹¹. Retinal vascular changes particularly proliferative retinitis is common in Hb SC disease and may lead to loss of vision. Approximately half the individuals with homozygous HbS disease experience vaso-occlusive crises with variable frequencies¹. Pulmonary hypertension is a high risk factor for early death^{13,14}.

In this case we found the child having 2 consecutive attacks at 3 months interval of pain in both the hip joints and cervical spine. This presentation may make confusion with septic arthritis, juvenile idiopathic arthritis and juvenile ankylosing spondylitis. The presence of sickle cell in peripheral blood film, positive sickling test and hemoglobin electrophoresis came to establish the diagnosis.

Hb electrophoresis differentiates homozygous Hb-S from heterozygous Hb-S. Hb capillary electrophoresis of this patient reveals a band which represent HbS and comprised of 77.8%, no HbA₁ and HbF was 19.6%. Therefore, the patient has also α^0 Thalassemia and the final diagnosis was Sick cell α^0 Thalassemia.

In SCD, hemoglobin usually remain in 5-9 gm/dl(7.7 in this case), Hematocrit is decreased to 17-29%(23.6% in this case), total leukocyte count is elevated to 12,000-20,000 cells/mm³ (19,240 cells/mm³ in this case) with a predominance of neutrophils, platelet count is increased(9,67000/cmm in this case), erythrocyte sedimentation rate is low, reticulocyte count is usually elevated¹⁷. Peripheral blood smears demonstrate target cells, elongated cells, and characteristic sickle erythrocytes. Other investigations like urinalysis, BUN, S. creatinine, arterial blood gas analysis, Secretory Phospholipase A₂(predictor of Acute Chest Syndrome), X ray chest and long bones, MRI of involved bony area (to differentiate between osteomyelitis and bone infarction), USG of whole abdomen(spleen, kidneys, gall bladder), Echocardiography (to detect Pulmonary hypertension)¹⁵ may be done. High granulocyte count is a risk factor for early death in SCD¹⁰.

The treatment mainly aims at symptom control and management of complications. This include management of vaso-occlusive crisis (Blood transfusion and hydration), chronic pain syndromes (NSAID, Morphine, Nalbuphine, Amitriptyline), chronic hemolytic anemia (Blood transfusion, Iron chelators, Folic acid, Vitamins), prevention and treatment of infections (pneumococcal, Hib & meningococcal vaccine, Penicillin prophylaxis, antibiotics mainly Macrolide and 3rd generation Cephalosporine)^{16,17,18}. Hydroxyurea 10-15 mg/kg/day increases HbF and subsequently reduces frequency of vaso-occlusive crisis. Management of some important complications include prevention of various organ damage by preventing tissue ischemia (blood transfusion, Aspirin), detection and treatment of pulmonary hypertension (Sildenafil, Bosentan)¹⁰.

Newer drugs like Phosphodiesterase type 5 inhibitor (Sildenafil) prevent and treat pulmonary hypertension and priapism, Endothelin receptor antagonist (Bosentan) treat pulmonary hypertension¹⁷. Experimental therapy includes 5-azacytidine, short chain fatty acid(Butyrate), antiadherent, antioxidants, anti-inflammatory therapy like Sulfasalazine, Dextran sulfate, IVIG, Corticosteroids. Glutamine, Clotrimazole, Arginine, low molecular weight heparin can play important role in management of SCD¹. Combination of two or more drugs, each with a different mechanism of action, would be additive and perhaps synergistic¹⁹.

Curative treatment is Bone Marrow Transplantation, Cord blood Stem cell transplantation although not routinely advised²⁰.

Prognosis is variable. Dactylitis in infants, low haemoglobin(<7gm/dl) and leukocytosis in absence of infections are predictors of adverse outcome⁵. Life expectancy is usually shortened²¹. Average life expectancy estimated is 42 years for males and 48 years for females²².

Conclusion

Sickle cell disease is not common in our country but whenever a child suffers from bone

pain and fever without any convincing etiology, sickle cell disease may be kept in the differentials and peripheral blood film should be checked.

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