Sickle Cell Disease[1]

Sajjad-ur-Rehman,* M.B., B.S., F.C.P.S.-II (Paed.) Trainee,
Postgraduate Medical Institute, Lady Reading Hospital, Peshawar, Pakistan

Summary

This is a case report of a patient who was admitted on clinical grounds as a case of Mitral regurgitation (due to Rheumatic heart disease) with Viral hepatitis but later on was diagnosed to be a case of Sickle cell disease.

Introduction

Inherited abnormalities of haemoglobin synthesis are divided into two groups: haemoglobinopathies and thalassemias. Sickle cell disease, a result of spontaneous genetic mutation, was first reported in 1910; it is the commonest type of haemoglobinopathy. It is clinically less evident as compared to Sickle cell anaemia and Sickle cell trait. It can present with protean manifestations e.g. cardiovascular, pulmonary and abdominal symptoms. Thus sickle cell changes in various organs can be confused with their organic diseases. Similarly, the latter can also occur concurrently in patients with Sickle cell disease. The possibility of such mutant disorder should always be considered while clinically evaluating patients with protean features.

Case Report

Mr. N. U., 15 years old boy, presented with attacks of joint pains and fever for the last 10 years and jaundice for the last one year. The joint pains, dull aching in character and present continuously, used to involve both knees and elbows but there was no associated swelling, hotness, tenderness or functional loss locally. The joint pains were not migratory in nature. The attacks, lasting for 3–4 days, used to resolve spontaneously and recurred after every 3–4 months. The accompanying fever was of high grade and was associated with generalised body aches and pains, headache and sometimes nausea and vomiting. There was no associated shivering, rigors or sweating and the fever used to subside spontaneously without medical aid, only to recur after 3–4 months.

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[1] Paper written by (late) Dr. Mukarram Shah, Associate Professor of Medicine, Khyber Medical College and Consultant Physician, Medical 'A' Unit, Khyber Hospital, Peshawar;
and
*Dr. Sajjad-ur-Rehman, then Senior House Officer, Medical 'A' Unit, Khyber Hospital, Peshawar.

The patient also had jaundice with yellow coloured sclerae and high coloured urine for the last one year. He had normal coloured stools and had no itching of the skin. The jaundice used to subside with medical treatment but relapsed as soon as the therapy was stopped. He had no other disease in the past and there was no family history of jaundice or any other illness. He was unmarried and economically poor. He was taking tab. Decadron and Jetepar at the time of admission with some improvement.

On examination, this intelligent and cooperative boy was found to have anemia and jaundice. His pulses, neck veins, fundi and B.P. were normal. The precardium was normal and apex beat not visible but palpable in the left 5th intercostal space, slightly to the left of the mid-clavicular line. There was no heave but a systolic thrill was present. First heart sound was soft at the apex and there was a pansystolic murmur at the mitral area radiating to the axilla. In the abdomen a non-tender, non-pulsatile liver with a smooth surface was palpable; spleen was two fingers enlarged and there was no evidence of ascites. Rest of the systemic examination did not reveal any significant finding.

A provisional diagnosis of Mitral regurgitation (MR) due to Rheumatic heart disease (RHD) with Viral hepatitis was made. Subacute bacterial endocarditis (SBE) was also considered in the differential diagnosis.

Investigations and Follow-up

The laboratory investigations showed an Hb of 10.5 Gm %, ESR 55 mm/Ist hr and a normal differential count. His urine, SGPT, prothrombin time, ASO titre, E.C.G. and blood cultures were all normal. Serum bilirubin was slightly elevated at 1.4mg%. Throat swab culture grew streptococcus pyogenes, sensitive to ampicillin.

Although high ESR, anemia and throat infection with streptococcus were in favour of RHD with SBE but negative blood culture and absence of any RBC in urine did not favour the diagnosis. Normal ASO titre was not taken as a negative finding because the patient was already on steroids. Almost normal SGPT, slight hyperbilirubinemia and negative bile salts/bile pigments in the urine did not favour the possibility of any serious acute parenchymal disease of the liver. But still such a possibility could not be ruled out because the patient was already on steroids. Since the two provisionally diagnosed diseases RHD (MR)/SBE and Viral hepatitis were quite serious in nature, therefore, no time could be spared in waiting for the confirmatory laboratory tests. To cover both the diseases, the patient was advised to have strict bed rest, fat free diet, plenty of glucose and was

given parenteral penicillin and streptomycin, and oral Ampiclox, Ascorbon, Surbex-T and Dijex. The steroids were continued in tailing doses.

Afebrile on the first two days, the patient started getting temperature (99.5–100°F) at irregular intervals on the 3rd day and at the same time complained of pain in both knees and elbows. The joints were found to be slightly hot and tender. Thinking it to be an acute rheumatic exacerbation, the patient was given tab. soluble Aspirin with milk and Mucaine, and the pain and fever subsided within the next four days. After that the patient remained clinically very well. During the first ten days, two clinical signs became less marked: first the palpable spleen started decreasing slowly and by the 10th day, it was not palpable; secondly the pansystolic murmur at the mitral area changed its character and became soft systolic murmur. At the moment both these events could not be explained easily. Repeat LFT's were normal except slight hyperbilirubinemia (2.2 mg%) which became 2.8 mg% after another two days. SGPT remained normal throughout. The ESR had fallen to 35 mm/Ist hr. As there was no evidence of liver damage, investigations for a possible haemolytic disease were carried out. His blood film, Coombs' test, X-ray skull and RBC fragility were normal. Tests done in Pakistan Medical Research Centre (PMRC) labs., Peshawar showed an HbF. at 7.5% (normal upto 2%) with positive acid elution and sickling tests. Reticulocytes were elevated at 14%. Electrophoresis, done in Armed Forces Institute of Pathologists, Rawalpindi, showed an abnormal band in the region of HbS. This confirmed the diagnosis of Sickle cell disease. At this juncture, folic acid was added to his treatment. His repeat ESR at this time had fallen to 9mm/ Ist hr. He was discharged home on the therapy mentioned above.

Follow up in three months revealed only a soft systolic murmur at the apex and a palpable liver; otherwise the patient was keeping well.

DISCUSSION

Inherited abnormalities of haemoglobin synthesis may be divided into two groups:-

(1) HAEMOGLOBINOPATHIES: associated with structurally abnormal haemoglobin varients.

(2) THALASSEMIAS: in which one or more of the normal haemoglobin polypeptides are synthesised at a markedly reduced rate.

Sickle cell disease is the commonest type of haemoglobinopathy. It was reported by James B. Herrick[6] in 1910 as "pedulia elongated, sickle shaped corpuscles" in a case of severe anaemia in a negro. In 1917, Emmel[6] observed process of sickling in vitro both in cases of severe anaemia and in those who e apparently healthy, thus recognizing both Sickle cell anaemia and Sickle cell t. In 1927, Hahan and Gillespie[6] discovered the conditions which could cause ling in vitro, including low oxygen. Thus they postulated the theory that it is in vitro hypoxia which causes the red cells in certain patients to become dis-ed and haemolysed.

Sickle cell disease, like all the other haemoglobinopathies, is an inherited ct. When a person is found to have inherited only one gene, he is referred as having Sickle cell trait. Such heterozygotes rarely manifest any clinically ificant phenotypic expression, therefore, in this sense they are recessive traits. they are not phenotypically silent because they can be detected by simple ratory tests. When a person has inherited two HbS genes, he is referred to aving Sickle cell anaemia. Such persons usually produce a significantly serious notypic expression. Sometimes one sickle cell gene is associated with a different ormal haemoglobin and thus the designation incorporates the names of both HbSC disease, HbS-thalassemia, HbSF disease etc.[5] All such conditions in ch HbS is associated with another abnormal haemoglobin genes and produces cal manifestations are called Sickle cell disease.

HbS is the result of the substitution of valine for glutamic acid at the residue of the β–polypeptide chain of haemoglobin. The gene of HbS occurs varying frequency in sub-Sahara Africa, Mediterranean countries, India and he descendants of people who have migrated from these regions: namely, roes in South, Central and North America. There is also a substantial inci-e of simultaneous heterozygosity for the HbS gene and one of the genes onsible for thalassemia or one of the other haemoglobinopathies such as HbS HbF.

The hallmark of Sickle cell disease is the presence of peculiar poikilocytes he blood which are sickle or oat shaped. Sickling is the result of deoxygena-of cells containing HbS. It is also favoured by a lowering of PH and by asing the temperature to that of the body.[3] Unsickling (reversion to a normal shape) occurs upon reoxygenation of the cells. Repeated sickling and unsick-deprives the cells of their ability to gain the normal biconcave discoid shape thus they become "irriversibly sickled cells".[6] Deoxygenation produces hae-lobin polymerization and sickling of the cells. What could be the nature of molecular interactions producing polymerization, is not completely under-

stood; but it is assumed that the substitution of valine for glutamic acid at β–6 creates a site, which when the molecule is deoxygenated, is capable of forming a bond with a complementary site on an adjacent molecule which may be non-HbS abnormal haemoglobin or even a normal molecule, whether in the oxygenated or deoxygenated state. While undergoing polymerization the capacity of HbS to react with other haemoglobin varies from one type to another.[6] Thus they copolymerize most effectively with another HbS molecule, and in decreasing order with HbC, D, E, A, J and F. Thus these findings profoundly effect the clinical picture of various combinations of HbS. Thus the patient with Sickle cell anaemia (with two HbS genes) have the most serious disease, followed by those with Sickle cell-HbC disease. On the other hand individuals, doubly heterozygous for HbS and hereditary persistence of HbF, whose cells contain 70% HbS and 30% HbF, rarely if ever have clinical disease.

When the cells become irreversibly sickled, they become liable to haemolysis and it has been estimated that about one third of the total cells destruction in Sickle cell anaemia takes place intravascularly due to fragmentation of relatively rigid sickled cells passing through the micro-circulation. The remaining two third of the haemolysis takes place extravascularly due to phagocytosis by macrophages in the spleen and other reticulo-endothelial organs.

The process of sickling leads to vascular occlusion typically in the micro-circulation because of 1) increase in whole blood viscosity which is due to the increase in the internal viscosity of each cell; and 2) inability of the relatively rigid sickled cells to alter their shape to the degree necessary to flow through capillaries, 4 Um in diameter or smaller. Vascular occlusion is more marked in those organs which are characterized by slow blood flow and high oxygen tension e.g. heart, spleen,bone marrow and placenta.

The age of onset of symptoms varies from 3 months to 15 years. One of the common symptoms in Sickle cell anaemia is the Sickle cell crisis which is described as an episode of moderate to severe pain, resulting from occlusion of portions of micro-circulation. Cardiovascular abnormalities are a constant feature of sickle cell disorder. Common cardio-respiratory symptoms include exertional dyspnoea, palpitation and pleuritis. All of the features of a hyperdynamic circulation may be observed. Such patients develop cardiac enlargement in early childhood and systolic murmurs, often pansystolic,[6] can almost always be detected. A loud third heart sound is almost invariably found. The radiological examination reveals cardiac enlargement of moderate to severe degree involving all the chambers. The ECG commonly shows abnormality but without any specific diagnostic finding.

The major acute pulmonary disorders in these patients are infectious and :cular occlusive episodes. These may occur separately or in combination and y be extremely difficult to distinguish from each other. Repeated attacks of h acute disorders may lead to chronic pulmonary disease including pulmonary ɔrial hypertension and cor-pulmonale.

Episodic abdominal pain due to vaso-occlusive crisis is a frequent feature : commonly involves liver, gall bladder and spleen. Stomach and intestine ɪn to be relatively infrequent sites of symptomatic disease. The spleen enlarges ing childhood without evidence of hyperfunction or hypofunction. Occasionally ing childhood the splenic sequestration syndrome occurs. In adult patients spleen usually has undergone repeated episodes of thrombosis, infarction and ɪsionally miliary calcification (autosplenectomy).[4]

The liver is usually enlarged but is not tender to touch. During sickle-cell is it may become acutely enlarged, tender and produce right hypochondrial ɪs and transient rubs. Such liver diseases as viral hepatitis, cholelithiasis, ; induced hepatitis and haemosiderosis occur with more frequency in patients ɪ Sickle cell disease.[6]

During childhood such patients may develop dactylitis (hand-foot syn-ne).[1] Bone marrow infarction is a common event. The joints are also involved number of disorders. Sometimes avascular necrosis of hip and shoulder s can occur due to vascular occlusion.

Genito-urinary involvement is rare and includes inability of the kidneys ɔncentrate urine, haematuria and sometimes nephrotic syndrome. They are all results of vaso-occlusive phenomenon.[6]

Nervous system involvement is also the result of vascular occlusive pheno-ɔn and the clinical manifestations include hemiplegia, convulsions, disor- of consciousness and visual disturbances.[4] The typical fundoscopic findings in ɛ cell disorders include tortuous looping (horse-shoe shaped) veins, micro-ɾysms and heavily pigmented areas of prior chorio-retinal infarction.[2]

Laboratory Findings : Three common procedures which aid in the labo-y diagnosis[1] of Sickle cell disease are:- 1) Blood picture; 2) Sickling ɔmenon and 3) Hb-Electrophoresis.

1) *Blood Picture :* Normocytic, normochromic anaemia is present during ntire life span of patients with Sickle cell disease. Poikilocytosis is always

present and the cells may be cigar-shaped, crescent like or ovalocytes and sometimes even acanthocytes and target cells. Decreased mechanical fragility and decreased osmotic fragility are usually present. The sedimentation rate in Sickle cell anaemia is consistently decreased.[6] The erythrocyte production may be impaired by folate deficiency, infection, ingestion of alcohol, medications, aplastic crisis or the prolonged administration of oxygen at high concentration. Leucocytosis, usually neutrophilia, is often present. Platelets are usually normal but may be decreased when there is folate deficiency or aplastic crisis. Bone marrow is hyperplastic with increase in erythroid mass and the presence of Sickle cells.[2]

2) *Sickling Phenomenon :* This is induced by deoxygenating the red cells by different manoeuvres. The degree and rapidity of this phenomenon depends upon the amount of sickle haemoglobin and the degree of deoxygenation.[4]

3) *Hb-Electrophoresis :* It is the single most useful laboratory procedure for the detection and identification of abnormal Hb. This method separates proteins according to their charge and thus each type of Hb can be identified.

Management : As the natural course of Sickle cell disease has never been comprehensively documented, the long term results of many therapeutic agents cannot be adequately evaluated. Many agents have been used but no single non-controversial agent has been found.[1] One of the least controversial and most effective therapeutic measure available is the blood transfusion. It can be in the form of repeated transfusions or exchange transfusion. Transfusion cannot be used for prophylaxis because of the problems of acquisition of compatible blood, transfusion reactions, hazards of serum hepatitis and iron overload; therefore they are best reserved for such severe clinical states as splenic sequestration syndrome, priapism, renal epistaxis, surgical procedures and cardiovascular and other life threatening complications. Exchange transfusion is preferable to repeated transfusions as it involves less risk of iron load and gives a better ratio of normal cells to sickle cells.

Attempts have been made to prevent or remedy the conditions which precipitate the vaso-occlusive crisis e.g. infection, dehydration, acidosis and perhaps cold as well.

Attempts to modify HbS chemically and reduce the chances of polymerization have not been beneficial. The use of urea and potassium cyanates for the prevention of vaso-occlusive crisis has not been successful on prolonged use.[4]

Although evidence of folate deficiency exists in patients with Sickle cell disease but whether or not such patients should receive daily supplemental doses of folic acid is controversial. But most authorities think it judicious to give 0.3 mg of folic acid daily, specially to patients who are pregnant or have deficient intake.[6]

CONCLUSION

Sickle cell disease is not necessarily found in Negroes but can be the result of spontaneous genetic mutation; it is clinically less evident as compared to Sickle cell anaemia and Sickle cell trait. It is particularly true when HbS is associated with HbF as in our case.

Sickle cell changes in the heart can be confused with organic disease particularly Rheumatic heart disease. Similar is the case with hepatic manifestations; also added is the fact that Viral hepatitis is more common in patients with Sickle cell disease.

Although such diseases as Rheumatic heart disease are not particularly common in patients with Sickle cell disease, yet there is no reason to believe that they cannot occur concurrently. Such was suspected in our case; but the only pitfall was that if the pansystolic murmur was due to organic lesion, how could it change its character?

Similarly high SGPT could not have been the result of concurrent Viral hepatitis, rather it was the result of Sickle cell crisis in the liver

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