Hemoglobinopathies are characterized by production of structurally defective hemoglobin due to abnormalities in formation of the globin part of hemoglobin. Some of the hemoglobinopathies which are common in our country are discussed below.

**SICKLE CELL ANEMIA**

The sickle hemoglobinopathies are hereditary disorders in which the red cells contain Hb S instead of Hb A. Hb S differs from Hb A in the substitution of valine for glutamic acid in the sixth position from the N terminal end of the beta chain. The solubility of Hb S in the deoxygenated state is ten percent that of Hb A. Thus in parts of microcirculation where flow rate is slow, cell transit is delayed and oxygen tension is low, the red cells sickle. This leads to further slowing of circulation and reduction in oxygen tension and more red cells sickle eventually leading to blockage of the vessel. This blockage is the cause of painful crisis observed in sickle cell disease.

**PREVALENCE**

Hb S is prevalent in tropical Africa. In India this condition is common among certain tribes in south India, Assam, Bihar and Orissa. It is also seen in certain communities in and around Aurangabad, Nagpur and Gujarat.

**CLINICAL FEATURES**

Though the condition is inherited and hence present since birth, clinical manifestations begin only after several months. This is because of Hb F present at birth which protects against sickling.

Anemia is present since early childhood. The child also has icterus and splenomegaly. A chronic anemic state is interspersed with acute episodes of painful crises during which the patient has severe pain in the limbs and even severe abdominal pain which can mimic acute appendicitis, pancreatitis or other causes of acute abdomen.

During childhood the spleen is moderately enlarged. Owing to repeated episodes of splenic infarction, spleen shrinks in size as the child grows so that in the adult patient with sickle cell anemia, spleen is usually not palpable.

Depending upon the site of blockage of microcirculation, the patient manifests with pain in that area as well as other symptoms, for e.g. Blockage of renal vasculature can lead to hematuria and loss of ability to concentrate the urine. Similarly involvement of pulmonary vasculature leads to episodes of pulmonary infarcts which may eventually lead to
pulmonary hypertension. Obstruction of blood flow to the penis can lead to priapism and to the head of femur can lead to avascular necrosis of femoral head.

Involvement of central nervous system is common in sickle cell anemia. Patient can present with monoplegia, hemiplegia, seizures etc. These episodes can be life threatening.

Chronic non healing ulcers over the leg is also commonly seen in patients with sickle cell anemia.

INVESTIGATIONS

Hemoglobin is usually low and the peripheral smear shows anisopoiikilocytosis, macrocytosis, presence of nucleated red cells, etc. Irreversibly sickled cells can also be seen in many cases. Reticulocyte count is usually increased. The platelet count is normal but there may be leucocytosis with shift to left, especially during crises.

Sickle test
Red cells containing Hb S become sickle shaped when mixed with a freshly prepared solution of sodium metabisulphite. The test is simple, easy to perform and detects both homozygous as well as heterozygous sickle cell disorders.

HEMOGLOBIN ELECTROPHORESIS

Although the peripheral smear and sickling tests demonstrate the presence of sickle cells, hemoglobin electrophoresis is essential for the diagnosis of sickle cell disorders as it can differentiate sickle cell trait from sickle cell anemia and also diagnose other coexistent conditions like sickle cell anemia and thalassemia etc. In homozygous sickle cell disease electrophoresis will show 60 – 80 % Hb S and the rest is Hb F and Hb A2 but Hb A is absent. In heterozygous sickle cell disease or sickle cell trait Hb S is 20 – 40 % and the rest is Hb A. In sickle –thalassemia Hb S and Hb F levels may be similar to sickle cell anemia but Hb A is also present.

TREATMENT

Continuous and effective general medical care and appropriate management of complications like crises as and when they arise form the mainstay of treatment in patients with sickle cell anemia. In view of increased erythropoietic activity to compensate for hemolysis, folate requirement is increased and therefore folate supplementation has been recommended.

Factors that promote sickling and predispose to crises should be avoided These include hypoxia, dehydration and acidosis. Exposure to cold and high altitude, excess fatigue should be avoided. Administration of pneumococcal and H influenza vaccine is recommended, especially in children less than 5 years of age. Malaria prophylaxis should be given in endemic areas and any infection should be treated promptly and vigorously with appropriate antibiotics.

Transfusions are usually not required, except in certain conditions like stroke, leg ulcers and intractable crises.

Treatment of crises: The principles of treatment are to keep the patient warm, to reduce pain, to avoid dehydration, to treat infection, hypoxia and acidosis. Partial exchange transfusion can be beneficial.

Surgery in a patient with sickle cell anemia: The patient is at increased risk during anesthesia. Scrupulous care is needed to avoid factors known to precipitate crises like hypoxia, acidosis, dehydration, circulatory stasis and infections. patients may also need partial exchange transfusions to reduce Hb S levels to 30 % or less.

Pregnancy and puerperium are potentially hazardous in mother with sickle cell disease. Patient should be carefully monitored and may require prophylactic transfusions and even exchange transfusions.

Marrow transplant in sickle cell anemia: Considerable number of patients with sickle cell anemia have undergone bone marrow transplantation but the decision of whether to transplant is a difficult one as the potential morbidity and mortality due to transplant is high.

Increasing the level of fetal hemoglobin: Hydroxyurea is known to increase fetal hemoglobin and hence prevent sickling. It has been extensively studied in clinical trials and found to significantly reduce the number and severity of crises. It should be remembered however, that all patients of sickle cell anemia are not candidates for hydroxyurea therapy.

SICKLE CELL TRAIT

When a person inherits only one gene for Hb S, he has sickle cell trait. Sickle cell trait is much less symptomatic compared to sickle cell anemia however on exposure to reduced oxygen tension, sickling can occur and lead to painful crises. Hence the patient needs to exercise similar kind of care to prevent crises and other complications.

Hematuria and inability to concentrate urine are commonly seen in these patients.

HEMOGLOBIN D

Hb D disease is common in Punjab. Patients with Hb D trait are asymptomatic and even in homozygous Hb D disease the anemia and hemolytic process are extremely mild and most patients are asymptomatic. The peripheral smear shows microcytosis and few target cells. Hb D has motility similar to Hb S on electrophoresis and is differentiated by negative sickling test.

HEMOGLOBIN E

Hb E disease is common in Bengal and Assam. Hb E trait is an asymptomatic condition whereas homozygous Hb E disease is associated with mild anemia and splenomegaly. Hb E and thalassemia produces a more severe clinical picture which resembles thalassemia intermedia or major.

HEREDITARY SPHEROCYTOSIS

It is one of the commonest hemolytic anemias. It is an autosomal dominant disease so that both males and females are equally affected. In most cases the patient is symptomatic since childhood, has jaundice and
hepatosplenomegaly. Patients may occasionally present with hemolytic, aplastic or infective crises. Many a times it is diagnosed when a young patient is being investigated to find out the cause of cholelithiasis.

The peripheral smear shows presence of spherocytes and diagnosis is confirmed by osmotic fragility test which demonstrate that the red cells hemolysate at higher saline concentrations than normal.

Splenectomy cures the anemia in majority of patients and hence is the treatment of choice in all patients with symptomatic anemia as it eliminates the need for repeated transfusions. Whether patients with compensated mild anemia or asymptomatic patients should undergo splenectomy is controversial.

Splenectomy is followed by rise in hemoglobin though spherocytosis persists.

**GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY**

It is present in about 5% of Indian population, with higher prevalence in certain communities like Parsee, Lohana, Bhanushali and Punjabi. It is inherited as sex linked recessive disorder hence males are usually affected with disease while females are asymptomatic carriers.

G-6-PD deficiency by itself does not produce any adverse effects, but when patients with G-6-PD deficiency are exposed to severe infections or certain medications, they develop severe hemolysis which can even lead to complications like oliguria, anuria and acute renal failure.

Medications which are known to cause hemolytic episode in these patients are analgesics like acetaminophen, phenacetin and acetyl salicylic acid, sulpha group of antibiotics, antimalarials like primaquine, quinine and mepacrine, antibiotics like nitrofurantoin, chloramphenicol, para amino salicylic acid etc. If any patient given these drugs complains of weakness, cola colored urine or oliguria or jaundice, he should be closely monitored for anemia and renal failure and the offending drug should be stopped. The patient may require transfusions, hydration and in severe cases with renal failure dialysis may be needed.

Persons with G-6-PD deficiency should be given the list of offending drugs which they should show to the doctor whenever they seek medical care in order to prevent hemolytic episode.

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**FIRST INTERNATIONAL STANDARD FOR COMMON GENETIC TEST APPROVED BY WHO**

The first international standard for a human genetic test was approved by the World Health Organization (WHO). Use of the standard will help to improve the accuracy and quality of laboratory results worldwide from a frequently used genetic test. This test identifies a genetic predisposition to thrombosis — a potentially life-threatening blood condition — and could therefore enable people to take preventive measures.

"Establishment of the first international standard for a genetic test is an important milestone. Genetic testing procedures are playing a vital and growing part in clinical medicine. This new standard will help to ensure that the tests are giving accurate results worldwide," said Dr David Wood, Coordinator of Quality Assurance and Safety of Biologicals at WHO.

The newly established standard, formally called an International Reference Panel, relates to the testing of patients for a particular genetic mutation known as Factor V Leiden. Discovered in 1994, this mutation is one of the most common genetic risk factors for venous thrombosis (blood clot), and is involved in 20-40% of all cases. Factor V Leiden induces a defect in the natural anti-coagulation system.

The test for Factor V Leiden is one of the most frequent genetic tests carried out in clinical laboratories. It determines the presence or absence of the mutation, which has been shown to result in a seven-fold to 80-fold higher risk of thrombosis depending on whether the individual carries one or two copies of the gene respectively.

The new standard was agreed at the 55th session of one of WHO's longest-standing committees, the WHO Expert Committee on Biological Standardization (WHO ECBS) which is meeting from 15 to 18 November in Geneva. It is composed of ten global experts from academia, industry and national regulatory authorities, as well as 25 advisors.

One of WHO's key functions, specified in its Constitution, is to develop, establish and promote international standards with respect to biological and other products. WHO is the world authority on biological standards, and has established more than 300 standards covering vaccines; blood products; therapeutic biological products, such as insulin; and diagnostic tests, such as those that detect HIV in a blood product.

Researchers are currently investigating whether or not there is a link between air travel and deep vein thrombosis. This is one example of a condition which may be more likely as a result of the Factor V Leiden mutation. Having information about their genetic make-up could allow travellers at risk to take additional precautions.

The standard for Factor V Leiden was