**HAEMOGLOBINPATHIES**

These are genetic disorders of haemoglobins

The genetic disorders of haemoglobin are divided into

1. Those in which there is a reduced rate of production of one or more of the globin chains, **the Thalassaemias which are the α and β**  thalassemias.

The thalassaemias are a heterogeneous group of genetic disorders of haemoglobin synthesis, all of which result from a reduced rate of production of one or more of the globin chains of haemoglobin.

1. Those in which there is a **structural change** in a globin chain leading to instability or abnormal oxygen transport: **structural Haemoglobin Variant includes the HbSS , HbAS, HbAC, HbSC etc.**

Structural haemoglobinopathy is a condition in which different haemoglobin variants are inherited which could lead to physiological or pathological phenotypic expression.The clinical features of sickle cell anaemia which is a pathologic structural Hb variant result more from the vasoocclusive consequences of sickle cells than from the anaemia itself. The clinical feauture includes hemolytic anaemia, acute chest pain, hand and foot syndrome,hepatosplenomegaly,bone deformities etc. Blood smears contain variable numbers of sickled forms, target cells, cigar-shaped cells, and ovalocytes.

1. In addition, there is a harmless group of mutations which interfere with the normal switching of fetal to adult haemoglobin production, known collectively as **hereditary persistence of fetal haemoglo**bin(HPFH); in many cases, these can be regarded as well-compensated forms of thalassaemia.
2. Some structural variants, HbE for example, are synthesized in reduced amounts and hence produce the clinical picture of thalassaemia.

**The Thalassaemias and related disorders**

The thalassaemias are the commonest single-gene disorders .They are a heterogeneous group of genetic disorders of haemoglobin synthesis, all of which result from a reduced rate of production of one or more of the globin chains of haemoglobin .

They are divided into the α, β, δβ, γδβ thalassaemias, according to which globin chain

is produced in reduced amounts. In some thalassaemias, no globin chain is synthesized at all, and these are called α° or β° thalassaemias, in others, designated α+ or β+ thalassaemias, the

globin chain is produced at a reduced rate. The δβ-thalassaemias are subdivided in the same way.

Because thalassaemia occurs in populations in which structural haemoglobin variants are common, it is not unusual to receive a thalassaemia gene from one parent and a gene for a structural haemoglobin variant from the other.

Furthermore, both α and β thalassaemia occur commonly in some countries, hence individuals may receive genes for both types. These different interactions produce a clinically diverse family of genetic disorders that range in severity from death *in utero* to extremely mild, symptomless hypochromic anaemias.

Clinically, the thalassaemias are classified according to their severity into major, intermediate and minor forms.

*Thalassaemia major* is a severe, transfusion-dependent disorder.

*Thalassaemia intermedia* is characterized by anaemia and splenomegaly, though not of such severity as to require regular transfusion.

*Thalassaemia minor* is the symptomless carrier state.

**Molecular pathology of thalassemia**

The main classes of mutations that cause thalassaemia are;

Deletions ,splice junction ,internal IVS, Nonsense ,frame shift,Exon 3 mutations.

 **Pathophysiology of Thalassemia (β- Thalassemia )**

The molecular defects in β- thalassaemia result in absent or a reduced chain production. α-chain synthesis is unaffected and hence there is imbalanced globin chain production, leading

to an excess of α-chains. In the absence of their partners, they are unstable and precipitate in the red cell precursors, giving rise to large intracellular inclusions that interfere with red cell maturation.

Hence there is a variable degree of intramedullary destruction of red cell precursors, i.e. ineffective erythropoiesis. Those red cells which mature and enter the circulation contain α-chain inclusions that interfere with their passage through the microcirculation, particularly in the spleen. The degradation products of excess α-chains, particularly haem and iron, produce a wide range of deleterious effects on red cell membrane proteins and lipids, which

are manifest by marked abnormalities of electrolyte homeostasis and membrane deformability. The end result is an extremely rigid red cell with a shortened survival.

Thus, the anaemia of β-thalassaemia results from both ineffective erythropoiesis and haemolysis. It stimulates erythropoietin production, which causes expansion of the bone marrow and may lead to serious deformities of the skull and long bones. Because the spleen is being constantly bombarded with abnormal red cells, it hypertrophies. The resulting splenomegaly, together with bone marrow expansion, causes a major increase in the plasma volume, which also contributes to the anaemia.

**Epidemiology of Thalassemia**

Thalassemia condition was first recognized in 1925 by a Detroit physician, Thomas B. Cooley, who described a series of infants who became profoundly anaemic and developed splenomegaly over the first year of life. In 1936, Whipple and Bradford, in describing the

pathological changes of the condition for the first time, recognized that many of their patients came from the Mediterranean region, and hence invented the word ‘thalassaemia’ from the

Greek meaning ‘the sea’. More recently, it has become clear that thalassaemia occurs widely throughout the world and that its clinical picture can result from the interaction of many

different mutations. The thalassaemias occur widely in a broad belt, ranging from the Mediterranean and parts of North and West Africa through the Middle East and Indian subcontinent to South-East Asia.

**Haematological changes**

Haemoglobin values on presentation range from 2 to 8 g/dL. The red cells show marked hypochromia and variation in shape and size, and many hypochromic macrocytes and misshapen microcytes, some of which are mere fragments of cells. There are always some nucleated red cells in the peripheral blood, after splenectomy they appear in large numbers. There is a slight elevation in the reticulocyte count. The white cell and platelet counts are normal unless there is hypersplenism. The bone marrow shows marked erythroid hyperplasia.

**Symptomatic treatment**

The symptomatic management of severe β-thalassaemia involves regular blood transfusion, the judicious use of splenectomy if hypersplenism develops, and the administration of chelating agents to attempt to deal with the problem of iron overload from regular blood transfusion.

**SICKLE CELL DISEASE**

Sickle cell disease is an inherited chronic haemolytic anaemia whose clinical manifestations arise from the tendency of the haemoglobin (HbS or sickle haemoglobin) to polymerize and

deform red blood cells into the characteristic sickle shape. This property is due to a single nucleotide change in the β-globin gene leading to substitution of valine for glutamic acid at position 6 of the β-globin chain . The homozygous state (HbSS or sickle cell anaemia) is the most common form of sickle cell disease, but interaction of HbS with thalassaemia and certain haemoglobin variants (Hb SC,) also leads to sickling.

**Geographic distribution of sickle mutation**

SCD is present in several locations within Africa (the Senegal, Benin and Bantu haplotypes) and Asia (the Arab–Indian haplotype). The sickle trait bestows survival benefit in areas endemic for falciparum malaria, and the distribution of SCD historically paralleled this disease. The sickle haemoglobin containing red cells inhibit proliferation of *Plasmodium falciparum*, and are more likely to become deformed and removed from the circulation. In recent times, the dissemination of the sickle mutation in different areas of the world took place from the movement of populations via trade routes and the slave trade

**Clinical Features**

The clinical features are of severe hemolytic anaemia punctuated by crises.The symptoms of anaemia are often mild in relation to the severity of the anaemia because Hb S gives up oxygen to tissues relatively compared to Hb A.The clinical expression of HbSS varies with some patients having an almost normal life free of crises but others develop severe crises even as infants and may die in early childhood or as a young adult.The SCD crises may be vaso occlusive crises , visceral sequestration crises ,aplastic crises and hemolytic crises.

**Laboratory Findings**

Reduced haemoglobin,anaemia,presence of sickled and target cells in blood film,positive sickling test, HbS band in electrophoresis.

**Treatment**

Folate,good nutrition,Crisis treatment by rest,warmth,rehydration,blood transfusion,use of hydroxyurea, Stem cell transplantation amongst athers.

**Sickle cell trait**

This is a benign condition with no anaemia , normal red cell appearance, presence of haematuria and 25-45% HbS.

Haemoglobin S can also be inherited with other Hbs such as Hb SC,Hb S/β-thalassaemia

Other Haemoglobins include Hb C, D, E, Constant Spring,