HEMOGLOBIN SYNTHESIS

# 1 Overview

*You know an idea about hemoglobin and its subtypes from biochemistry!*

Hemoglobin contains 4 heme groups, each carrying 1 iron atom, and each iron atom binds to 1 O2 molecule.

(1 hemoglobin 🡺 4 iron atoms) in contrast to transferritin (2 iron atoms)

* Our body Heamoglobin is
  + **Hb A (major)**: containing 2 α and 2 β subunits (α2β2),
  + **Hb A2:** delta subunits instead of β (α2δ2)
  + **Hb F:** gamma subunits instead of β (α 2γ2). It is a fetal hemoglobin that is present in adults in minor amounts.
  + Other Hemoglobins (Hb Gower1 and 2 and Portland) are present at different stages in embryonic and fetal life.
* Abnormal Hemoglobin
  + **Hb S:** mutation at position 6 of the β subunits
    - (glutamate 🡪valine)
  + **Hb C:** (glutamate 🡪 lycine) *also at position 6 mutation of* β

## Heamoglobinopathies

They are diseases caused by reduced or abnormal synthesis of hemoglobinn

* Synthesis of abnormal hemoglobin like sickle cell disease.
* Reduced rate of synthesis of normal alpha (α) or β globin chain (Alpha (α) and β thalassemia).

## Epidemiology:

* Affects10% of the world's population.
* Occurs in tropical and subtropical areas.
* Beta (β) thalassemia is more common in the Mediterranean region.
* Alpha (α) thalassemia is more common in the Far East.

We will take **thalassemia** and **sickle cell anemia.**

# fig THALASSEMIA:

Thalassemias are a heterogenous group of genetic disorders, which result from a reduced rate of synthesis of α or β chains due to reduced, absent or depleted

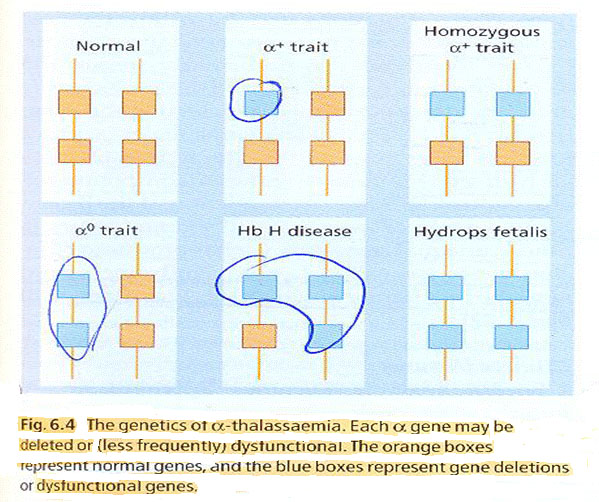
**Mode of inheritance:** autosomal recessive

## A- ALPHA THALASSEMIA:

* Caused by deletion of one or more of the 4 genes encoding for the α globin
* Since there are four copies of alpha (α) globin gene, the clinical severity depends on the numbers of genes missing.

### HYDROPS FETALIS:

* There is loss of all 4 genes, so there is complete suppression of alpha (α) chains 🡪 fetus incompatible with life 🡪 intrauterine death.



### HEMOGLOBIN H DISEASE:

* There are 3 gene deletions. Moderately severe anemia 7 – 11 g / dL.
* Microcytic hypochromic anemia.
* Splenomegaly.
* Hb H is formed (composed of 4 beta chains - β4) and can be seen in the peripheral blood by reticulocyte stain or can be detected by Hb electrophoresis.
* Henz body can be found
  + *They are inclusions within RBCs composed of denatured Hb.*

### ALPHA THALASSEMIA TRAIT:

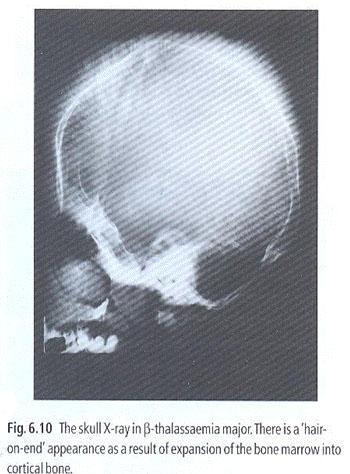
* Loss of 1 or 2 genes.
* No anemia but the RBC count is increased and there is microcytosis (decrease MCV) and hypochromia (decrease MCH). This is important in differentiation with iron deficiency anemia.
* Hemoglobin electrophoresis is normal.
* Diagnosis is based on α:β chain synthesis. Normal ratio is 1:1. It is reduced in α thalassemia and increased in β thalassemia.

## B. BETA THALASSEMIA

* No B chain (β0) or small amounts (β+) are synthesized.
* Alpha (α) chain production in excess 🡪 precipitate in RBCs 🡪 hemolysis
* Production of gamma (γ) chains reduced severity of the disease by taking up the excess α chains
* The defect is gene mutation rather than a gene deletion (unlike α)
* HbF is increased especially in β0

### Clinical features:

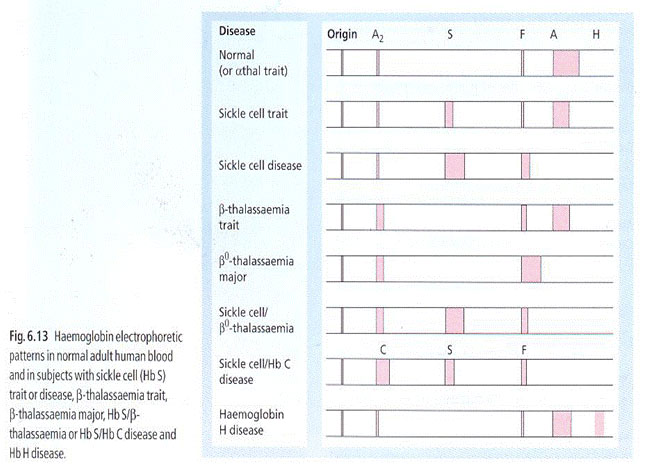
1. **Anemia**: Severe, appears 3-6 month after birth (switch from γ to β chains).
2. **Hepatomegaly – Splenomegaly**: due to hemolysis, extramedullary hematopoiesis and iron overload "see no. 5 for more".
3. **Jaundice**: Due to hemolysis, liver damage.
4. **Bone expansion**: due to marrow hyperplasia results in thalassemia facies, bossing of skull, and hair on end appearance on x –ray.



1. **Iron overload:** due to hemolysis, increased absorption and multiple transfusions results in:
2. Hepatomegaly and liver damage.
3. Splenomegaly.
4. Endocrine organs failure: growth failure, delayed puberty, diabetes mellitus, hypothyroidism.
5. Cardiac complications: usual cause of death if not treated “arrhythmia due to accumulation of iron in heart”

Treatment: deforaxamine, or any method that kicks iron out of body.

1. **Increased susceptibility to infections:** usually bacterial infection especially after splenectomy 🡪 Pneumococcal, Meningococcal and Hemophilus. **MCQ**



### Lab diagnosis

1. **Anemia:**

* Hypochromic microcytic (low MCH, low MCV).
* Reticulocytosis.
* On peripheral blood smear: nucleated RBC “normoblasts”, target cells, polychromasia, basophilic stippling.

1. **Hemoglobin Electrophoresis:**
   1. **HbA:** absent. ***MCQ***
   2. **HbF:** Increased.
   3. **HbA2:** Normal, decreased, increased.
   4. Α : Β globin chain ratio is increased.

### Beta-THALASSEMIA TRAIT (THALASSEMIA MINOR):

* Common, symptomless.
* **Laboratory findings:**
  + Microcytosis (low MCV), Hypochromia (low MCH).
  + Mild anemia. “or no”
  + Increased RBC count.
  + Increased HbA2 level. > 3.5%
* It is important to diagnose the trait in pre-marital counseling and prenatal diagnosis, because if both parents with B thalassemia trait, 25% chance of a child with thalassemia Major.
* **Prenatal diagnosis:** 
  + Chorionic villous sampling.
  + Amniotic fluid analysis.
  + Fetal blood sampling.

### THALASSEMIA INTERMEDIA:

* Moderate severity, Hb7 -10 g / dL.
* caused by a variety of genetic defects e.g.:
  + Homozygous B thalassemia with increased HbF-gamma (γ).
  + Homozygous mild B thalassemia – mild defect in B chain synthesis.
  + **Hemoglobin lepore:** abnormal hemoglobin caused by crossover of the beta (B) and delta (δ) genes, causing partial deletion of both genes.

# Sickle Cell Anemia

Sickle cell disease is a group of hemoglobin disorders in which there is an inherited defect in the beta–globin gene. It is a “qualitative” hemoglobin abnormality, unlike thalassemia which is quantitative.

* caused by a variety of genetic defects in the beta globin and instead of it form:
  + homozygous sickle cell anemia (Hb SS): the most common form. It is serious and fatal !
  + Double heterozygous Hb SC (rare)
  + Double heterozygote HbS B thalassemia. “less common”

## Hemoglobin S

* The most common Hb Abnormality
* Substitution of valine for glutamate in position 6 in the B chain.
  + Hb a2B(­s)2
* The hemoglobin becomes less soluble, and precipitate when O2 is depleted 🡺 cystic formation.

### Pathogenesis:

Deoxygenated sickle hemoglobin polymerizes into long fibers. The RBCs sickle:

* Hemolysis due to fragility.
* Blockage of vessels  infarct.
* High viscosity.

### Epidemiology:

* Widespread.
* 1/4 in West Africa. Protection against malaria is afforded by carrier state.
* In Saudi Arabia: common especially in Eastern Province, Jizan and Al-Ola area.

### Factors affecting sickling

* 1. Oxygen tension
     1. 50-60 mmHg for SS
     2. 20-30 mmHg for AS
     3. pH
     4. Inhibited at Alkine
     5. Exacerbated by acidification
  2. concentration of HbS
  3. presence of other Hb

### Clinical Features

1. **Severe hemolytic anemia:** however the symptoms are mild compared to the Hb level because HbS has a lower affinity for Q2 than A2. The symptoms are pallor, jaundice … etc. MCQ
2. **Crises:** MCQ
   1. **Vasoocclusive:**
      1. Painful.
      2. Precipitated by infection, acidosis, dehydration, pyrexia, deoxygenation, exposure to cold, pregnancy.
      3. Organ infarcts e.g. bone (femoral head necrosis), lungs, spleen, liver, brain (stroke).
      4. Painful dactylitis – small infarcts of the small bones of the hands and feet.
   2. **Visceral Crises (Sequestration):**
      1. Pooling of blood.
      2. Sickling inside the organs e.g. spleen, liver and lungs (acute chest syndrome). MCQ
   3. **Aplastic Crises:**
      1. Due to parvovirus infection or folate deficiency.
      2. Sudden fall in Hb, associated with decreased reticulocyte count.
   4. **Hemolytic Crises:**
      1. Increased rate of hemolysis.
      2. Decreased Hb with increased reticulocyte count.
3. **Other:**
   1. Susceptibility to infection, e.g. Salmonella osteomyelitis. MCQ
   2. Gall stones.
   3. Liver damage.
   4. Papillary necrosis of the kidney 🡪 hematuria.
   5. Leg ulcers.
   6. **Splenomegaly** in early childhood and autosplenectomy in later life (asplenia). MCQ
   7. Retinopathy.
   8. Osteomylitis 🡪 infection of bones lead to deformation 🡪 hand foot syndrome

### Factors predisposing crises:

* + - 1. Infection
      2. Pyrexia
      3. Exposure to cold
      4. Dehydration
      5. Pregnancy

### Laboratory findings:

* Hb: Usually 6 -9 g /I.
* Peripheral blood smear: Sickle cells, target cells.
* Sickling test: Positive (test of solubility of Hb when deoxygenated). ***MCQ***
* Hb electrophoresis: The predominant Hb is HbS. HbF (5 – 15%). Higher values of HbF associated with milder disease. ***MCQ***

### SICKLE CELL TRAIT:

* No anemia.
* Normal RBC morphology on peripheral blood smear.
* Very minimal infarction e.g. kidney 🡪 hematuria. ***MCQ***
* HbS level = 25 – 45%.
* Sickling increase when exposed to O2 e.g. anesthesia, pregnancy, high altitude.