Hemoglobinopathies

Decrease of production of globing chan or producing abnormal globin chan

Hemoglobinopathies are types of intracorpuscular defects leading to the production of an abnormal hemoglobin or to an aberration of hemoglobin synthesis

Mutations in gene itself

Decrease of production , Complete absence or complete loss of the function of one of the gene (related to the amount of globin chan which will be produced)

Abnormal hemoglobins

- Most are clinically insignificant with no physiologic consequence

- Most abnormalities occur in the β chain with abnormalities in this chain more likely to cause disease because we have only two genes that encode the β chains, but we have four genes that encode the α chains.

- Most variants arise from the substitution of a single amino acid in the β globin chain.

- Changes may also arise from multiple substitutions, insertions or deletions, frame shift mutations, cross-over, and fusions of subunits.

Mutations dose not mean there's complete loss of the function of the gene , according to the site of mutations we will have less activity of the gene , less transcription, less production of protein.

production of some globin chan هناك لكن ما زال mutations في

- If an individual is homozygous for a structural gene in the β chain, the individual is said to have the disease or anemia
- If the individual is heterozygous, they are said to have the trait, and 50% or less of the hemoglobin will be abnormal.

Sickle cell disease

It's called point mutation : change in one nucleotide lead to change in genetic code of glutamic acid (hydrophilic) to genetic code of Valine (hydrophobic)
Glutamic Acid ع the valine hydrophobic
The globin Chan that surround heme molecule it's in helical conformation,there some of the AA of glob in Chan protruding outside (hydrophilic) ع. another hiddden inside (hydrophobic)

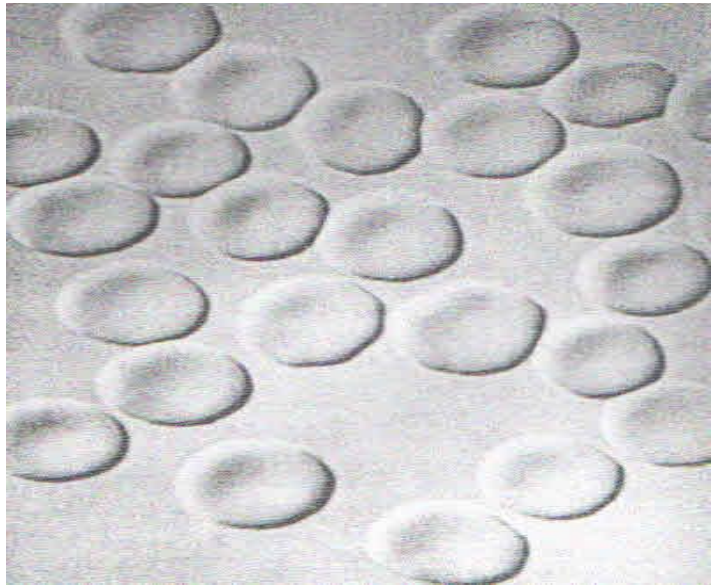
- Hemoglobin S: position 6 on the β chain has a valine (nonpolar) substituted for the normal glutamic acid (polar).
- Carriers of the gene, when parasitized by Plasmodium (causes malaria), cells containing HbS will sickle quickly, either killing the parasite or causing RBCs to be sequestered in the spleen and destroyed.

The life span of rbc is shorter from 2 to 3 weeks it's half of the duration to malaria to complete life cycle

- Therefore, having the gene provides a certain protection against malaria.

Pathophysiology of the disease

- When oxygenated, Hb S is soluble, but when oxygen tension decreases, Hb S in the deoxyhemoglobin state polymerizes into insoluble aggregates leading to sickled cells.

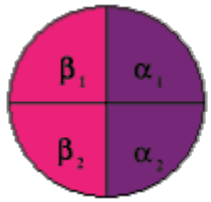


- This leads to increased blood viscosity which leads to decreased circulation and increased exposure to low oxygen.

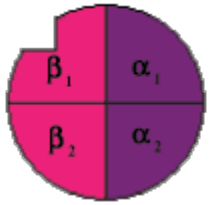
- This, in turn, leads to more sickling.

- The small microvasculature may become clogged with the rigid sickle cells leading to hypoxia and infarction of organs and a "sickle cell crisis".

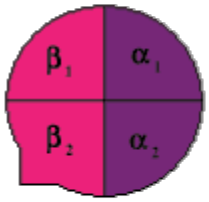
Molecular changes of HbS



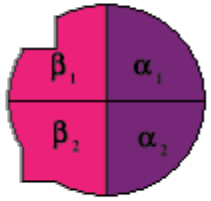
Oxyhemoglobin A



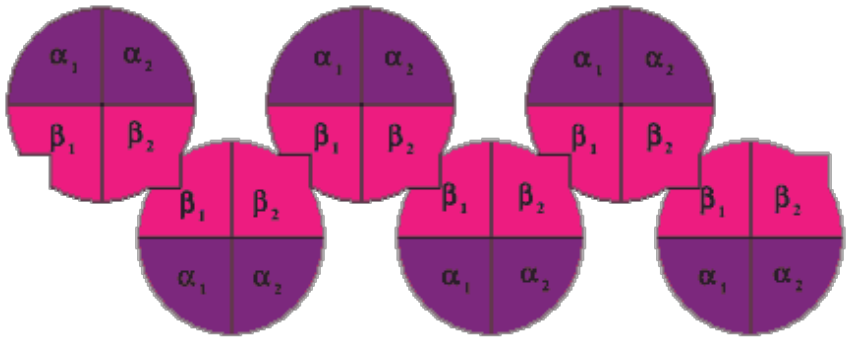
Deoxyhemoglobin A



Oxyhemoglobin S



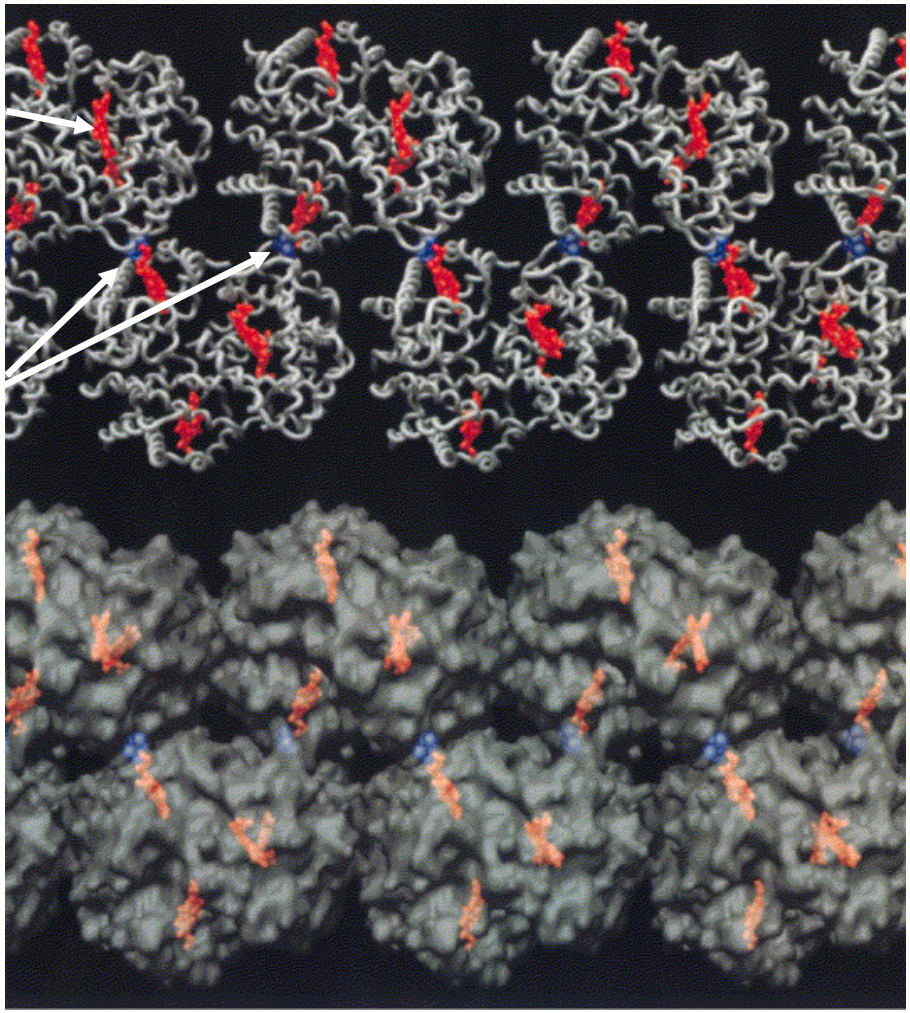
Deoxyhemoglobin S



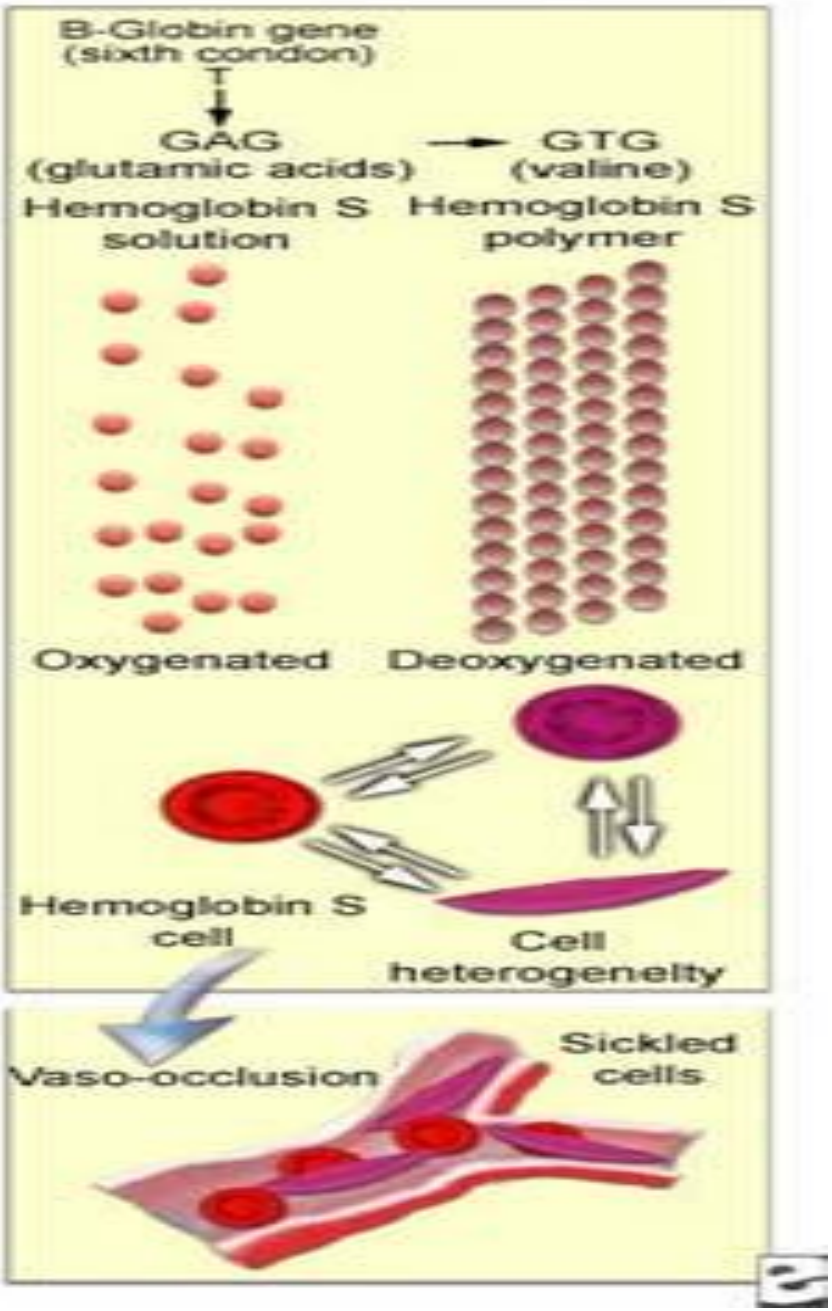
Deoxyhemoglobin S polymerizes into filaments

Heme

Valine



Molecular and cellular changes of HbS



Decreased PO_2

Permanent damage to RBC

Cell ⇔ endothelium interactions

- Upon reoxygenation, the RBC may return to its original shape.
- With repeated sickling damages the permeability of the RBC membrane leading to premature death of the cell.

- In addition, after repeated sickling events, the cells become irreversibly sickled and are removed by the spleen.

- Early in childhood, the spleen loses its function due to splenic atrophy and necrosis from repeated ischemic (blood supply decreased due to blockage of the small vasculature) crises.

-Thus, these young patients are more subjected to infections.

Because the spleen is a part of immune system

-The liver and bone marrow then take over destruction of abnormal cells.

-Hb S has a decreased affinity for oxygen, leading to a shift to the right in the oxygen dissociation curve.
- This, however, creates more deoxyhemoglobin, and hence, more sickling.

Clinical findings

-The disease is diagnosed early at about 6 months of age when hemoglobin F is replaced with Hb S rather than Hb A.
- Homozygous individuals frequently do not live beyond middle age.
- Chronic hemolytic anemia.
- RBC survival may decrease to 14 days.
- Increased bilirubin turnover leads to gallstones.

Lab findings

The main differential feature sickle cell is shape

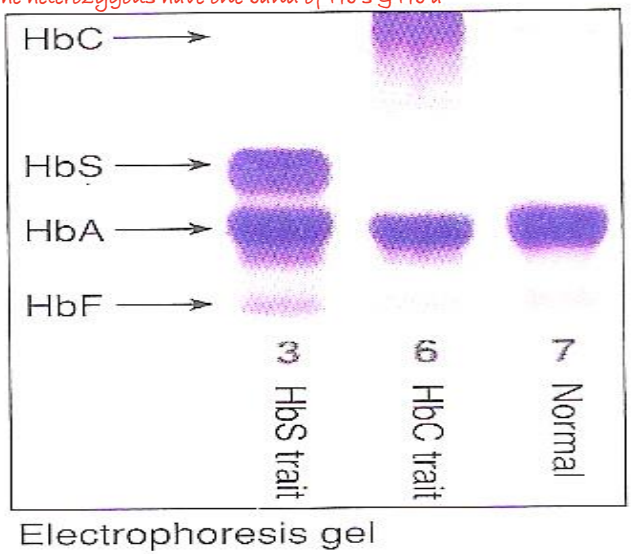
- Normochromic, normocytic anemia (6-10 g/dl Hb).
- 10-20% reticulocytes
- RBCs are sickled cells
- Bone marrow: normoblastic hyperplasia

Diagnosis: peripheral blood smear, Hb electrophoresis, solubility tests, sodium metabisulfite will cause the cells to sickle by deoxygenating the blood.

If we take blood film from the patient in good oxygenation state we can't see sickle cells anemia

The best method for investigation of genetic disease is a genomic study

If we have a petient with homozygos Hb s we will see a one band Pattern
The heterozygous have one band of Hb s & Hb a



Electrophoresis gel

Therapy

- No known effective long term therapy, hoping to develop drugs that can inhibit Hb S polymerization
- Bone marrow transplant
- Gene therapy

Sickle cell trait (heterozygous for Hb S)

-Usually the patient has no problems because >50% of their hemoglobin is Hb A with some occasional problems upon exposure to severe hypoxia

Diagnosis: Hb electrophoresis or ttt with sodium metabisulfite

Hemoglobin C disease

- Lysine is substituted for glutamic acid at position 6 on the β chain.
- Hb C has decreased solubility and in the deoxyhemoglobin state, the RBCs form intracellular crystals leading to a rigid RBC with a decreased survival time (33-35 days).
- The disease is usually asymptomatic.

Lab findings

- Slight ↑in reticulocytes
- Hb C crystals

Diagnosis: Hb electrophoresis

S/C disease

- Both β chains are abnormal, therefore, Hb A is absent and the disease is almost as severe as in Hb S disease
- Clinically, it is similar to those of mild sickle cell anemia
- Can be differentiated from Hb S by Hb electrophoresis.

Hb D disease and trait

- A glutamine replaces glutamic acid at position 121 on the β chain
- Both homozygous and heterozygous states are asymptomatic
- When combined with S to form D/S, D potentiates the polymerization of deoxyhemoglobin leading to sickling and mild anemia.

Hb E disease and trait

- A glutamic acid replaces lysine at position 26 on the β chain leading to a slightly unstable hemoglobin with oxidant stress.
- Hb E has a decreased affinity for oxygen leading to a shift to the right in the oxygen dissociation curve
- Homozygous individuals have a mild microcytic anemia with decreased RBC survival, target cells and increased osmotic fragility
- Heterozygous individuals are symptomless

Unstable hemoglobin disorders

- Contain amino acid changes in internal portions of Hb chains leading to decreased stability
- They are characterized by precipitation of the abnormal Hb as Heinz bodies which leads to increased cell rigidity, membrane damage, and RBC hemolysis.
- They are only found in the heterozygous state since the homozygous state is incompatible with life

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Hemoglobin variants with altered oxygen affinity

- Amino acid substitutions in the globin chains close to the heme pocket may affect the ability of the hemoglobin to carry oxygen
- This also occurs with substitutions near the 2, 3 DPG binding site

Hb M variants

- Are characterized by permanent methemoglobin formation because iron is stabilized in the Fe $^{+3}$ state.

Because mutations in the gene encoding methemoglobin reductase or glysraldehyde 3 phosphate dehydrogenase that produce NADPH which use to convert the methemoglobin to hemoglobin.