كلمتان خفيفتان على اللسان ، حبيبتان الى الرحمن ، ثقيلتان في الميزان : سبحان الله وبحمده ، سبحان الله العظيم 🌹🌿

Hemoglobinopathies

تبييض وحوسبة : عبادة العايد

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

خلل / انحراف و

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. → also known as "point mutation"

Note 1 : Point mutation = one nucleotide substituted by other .. • which lead to (silent , non-sence , missence mutations)Silent = same amino acide Missence = other amino acid Non-sence = most dangerous , stop codon

الحمدلله

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

Hb ---> Externally it is watery , internally it is waxy .

- 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 glutamic acid ⟶ Valine

- 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. → benifit of sickle cell anemia see note 2 next slide
- Therefore, having the gene provides a certain protection against malaria.

: 2NOTE

days40 It is because --→ life cycle of malaria take place in

days)14 weeks (2 But the lifespan of sickled cell is

. t continue its life cycle and it will die’So parasite can

. Also sikled cell will sequestered the parasite and kill it

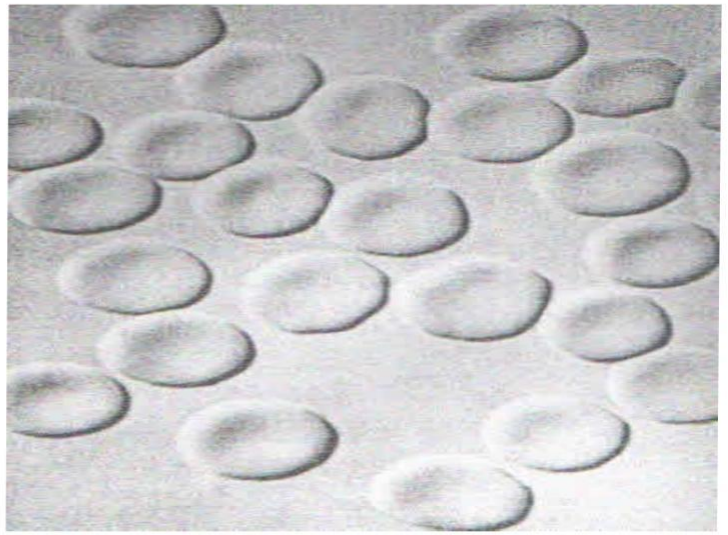
Pathophysiology of the disease

soluble → insoluble

- 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.

deoxygenation → Polymirization → aggregation → sickling

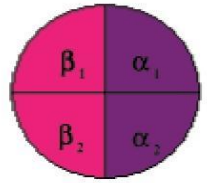
- This leads to increased blood viscosity which leads to decreased circulation and increased exposure to low oxygen.



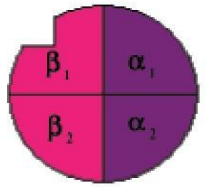
- This, in turn, leads to more sickling.

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

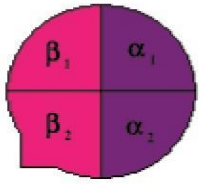
Molecular changes of HbS



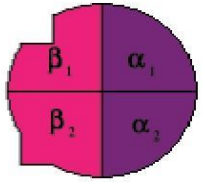
Oxyhemoglobin A



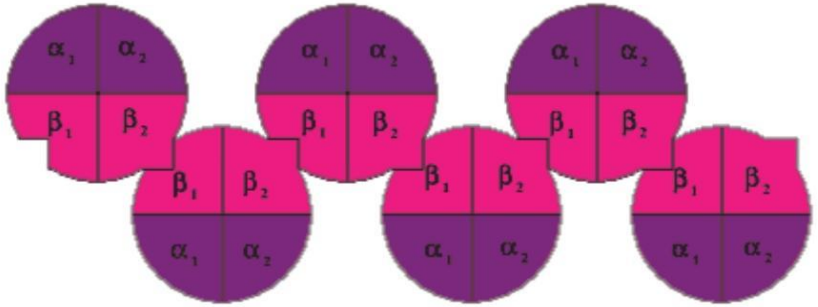
Deoxyhemoglobin A



Oxyhemoglobin S



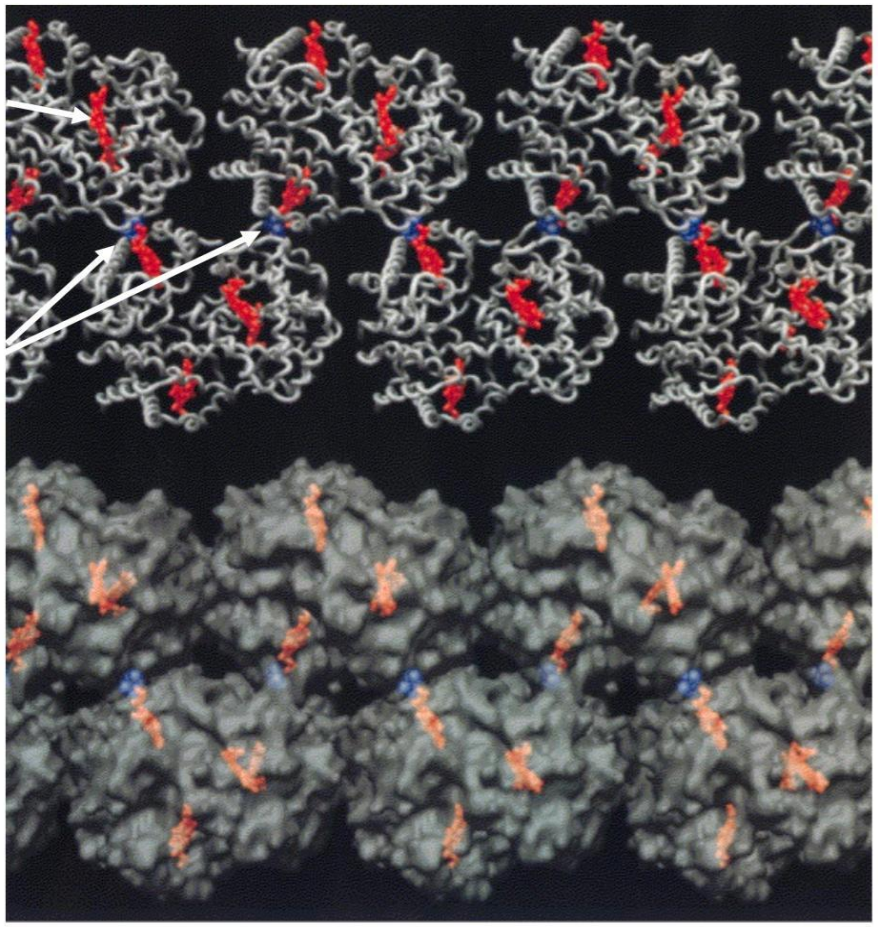
Deoxyhemoglobin S



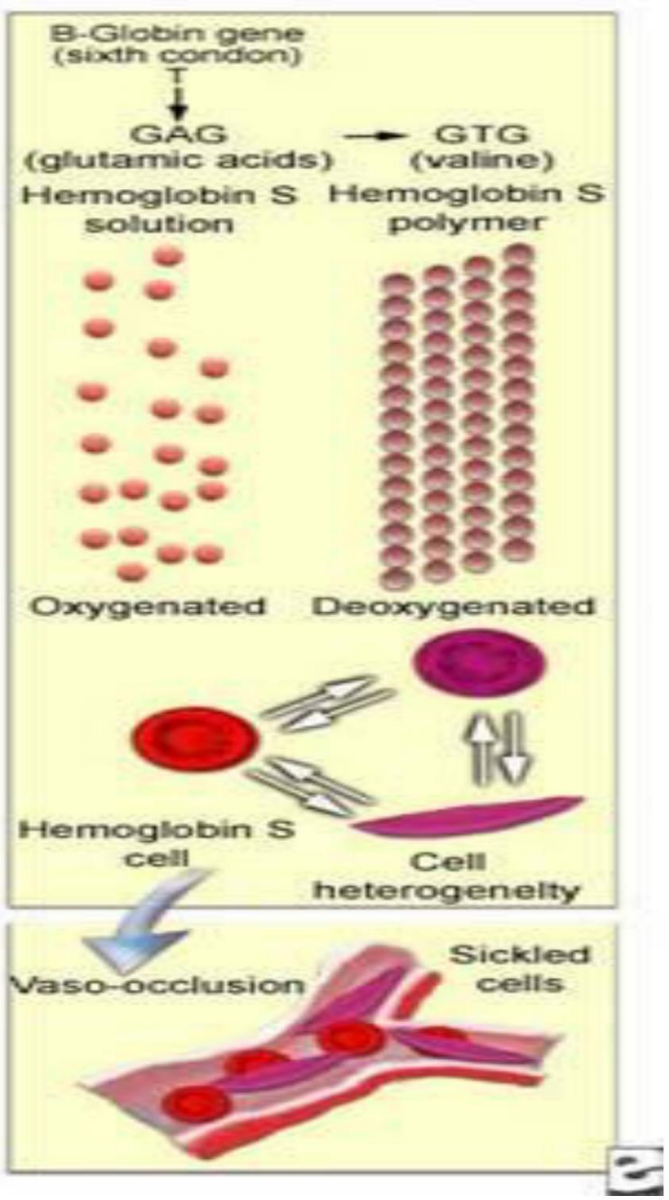
Deoxyhemoglobin S polymerizes into filaments

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.

-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

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

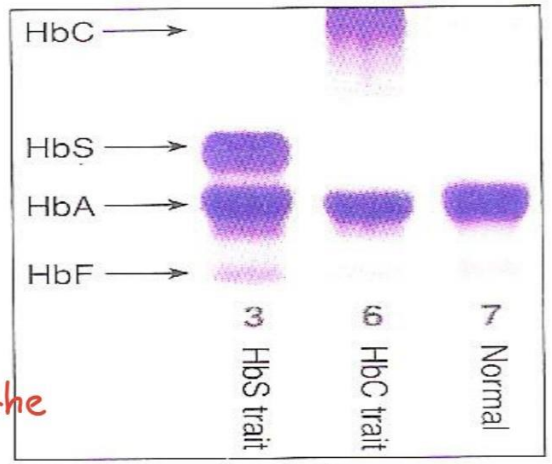
صل على رسول الله

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

best method

Therapy

- No known effective long term therapy, hoping to develop drugs that can inhibit Hb S polymerization
- Bone marrow transplant → not available all the time but it is the most effective
- Gene therapy



Electrophoresis gel

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

سبحان الله
وبحمده

Hemoglobin C disease

glutamic acid → Lysine

- 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.

سبحان الله العظيم

Hb D disease and trait

glutamic 121 acid → glutamine

- 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

lysine → glutamic acid

- 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

الله أكبر ولله الحمد

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

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 → so it affecting all cells because it affect all metabolic Pathways which require O_2 to be activated.
- This also occurs with substitutions near the 2, 3 DPG binding site

Hb M variants

→ may be because → mutation in gene encoding methemoglobin reductase enzyme
→ mutation in GAP dehydrogenase enzyme ⇒ because it produce NADH & NADPH

reaction 6 in glycolysis ← glyceraldehyde-3-phosphate

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

لا حول ولا قوة
إلا بالله

NOTE 3 :

We can distinguish between types of hemoglobin (A , S , C , D , M ... etc) by :

1) PB smear to see features
2) electrophoresis , which also can determine whethere mutation are homozygous or heterozygous .

1) Hb S = glutamic acid (6) ⟶ valine (Polar ⟶ non Polar)

2) Hb C = glutamic acid (6) ⟶ lysine (decrease solubility)

3) Hb D = glutamic acid (121) ⟶ glutamine (potentiate Polymirization if combined with Hb S)

4) Hb E = lysine (26) ⟶ glutamic acid (-unstable with oxidant stress
-shift O_2 dissociation curve to right = releas = low affinity to O_2)

ريكورد جديد
مختلف عن
السابق

Thalassemias

-They are a heterogeneous group of genetic disorders with variable levels of severity.

- Individuals with homozygous forms are severely affected and die early in childhood without treatment

- The disorders are due to mutations that decrease the rate of synthesis of one of the two globin chains (α or β).

- The genetic defect may be the result of: NOTE 4 next slide

- A mutation in the noncoding introns of the gene resulting in inefficient RNA splicing to produce mRNA, and therefore, decreased mRNA production

-The partial or total deletion of a globin gene

- A mutation in the promoter leading to decreased expression

- A mutation at the termination site leading to production of longer, unstable mRNA

- A nonsense mutation.

Mutations of alpha & beta because :

1. Mutation in the non-coding reagion which will affect the process of intron splicing .

Intron splicing : post-transcriptional modification in which the introns spliced and substituted by exons which lead to continues transcription .
** introns are non coding , and exons are coding .

2. Partial or complete loss (deletion) of one gene (either alpha or beta) .
It is more dangerous on beta chains because we will loss more than 50% of its activity (because there are just 2 genes encode it)

3. mutation in promotor :
- it is dangerous because there is complete absence in the gene expression , because it is the region which will recognized and initiate transcription .
- it is similar to criggler-najjar syndrome I , because there are mutation in promotor region

4. Mutation in termination side of the gene ----> lead to prolonged mRNA ----> short life time
Because it is elongated so it don't have protection and correction , so it will degraded fastly .

5. Non-sence mutation ----> lead to stop codon , which is associared with premature termination of protein synthesis .

سبحان الله

- Any of these defects lead to:
- An excess of the other normal globin chain see NOTE 5
- A decrease in the normal amount of hemoglobin made
- Development of a hypochromic, microcytic anemia

β thalassemia

- The disease manifests itself when the switch from γ to β chain synthesis occurs several months after birth.
- There may be a compensatory increase in γ and δ chain synthesis resulting in increased levels of Hb F and A_2.
- The genetic background of β thalassemia is heterogeneous and may be roughly divided into two types:
  1- β^0 in which there is complete absence of β chain production which is common in the Mediterranean.
  2- β^+ in which there is a partial block in β chain synthesis.

- At least three different mutant genes are involved:
  β^{+1} →10% of normal β chain synthesis occurs
  β^{+2} → about 50% of normal β chain synthesis occurs
  β^{+3} →50% of normal β chain synthesis occurs see NOTE 6

لا إله إلا الله .

NOTE 5 :

Deficincy in one chain in thalassemia will compensate by other type , so it lead to abnormal situation which short life span of RBCs and hemolysis .

NOTE 6 :

If there 2 genes produced 100% of protein synthesis , if one gene is mutated , the other gene can't produce coplete activity and activate 50% of protein never , because of unfavourable lionization which lead to less than 50% percent of the activity .

رب اغفر لي

- The clinical expression of the different gene combinations (1 from mother and 1 from father) are as follows:
- β^0/β^0, β^{+1}/β^{+1}, or $\beta^0/\beta^{+1,+2,or\ +3}$ = thalassemia major (Cooley's anemia), the most severe form of the disease. stage 1

- Imbalanced synthesis leads to decreased total RBC hemoglobin production and a hypochromic, microcytic anemia.

- Excess α chains precipitate causing hemolysis of RBC precursors in the bone marrow leading to ineffective erythropoiesis causing severe anemia.

- In circulating RBCs, α chains may also precipitate leading to pitting in the spleen.
- Untreated individuals die early, usually of cardiac failure (due to overwork and hemochromatosis). see NOTE 7

: 7NOTE

Hemochromatosis caused by increase of iron in liver , this will lead to cardiac myopathy and liver cell faliure which will progress to hepatocellular carcinoma .

أستغفر الله
وأتوب إليه

- Lab. findings include:
  - hypochromic, microcytic anemia
  - basophilic stippling from α chain precipitation
  - increased reticulocytes and nucleated RBCs

- Serum iron and ferritin are normal to increased and there is increased saturation

TIBC is important to mesure to distinguish between IDA and other anemieas , it will be high in IDA ...
Also degree if hemolysis distinguished .

- Chronic hemolysis leads to increased bilirubin and gallstones
- Hemoglobin electrophoresis shows increased Hb F, variable amounts of Hb A2, and no to very little Hb A

-Therapy: transfusions plus iron chelators to prevent hemochromatosis and tissue damage from iron overload, beside the trials of gene therapy.

{ قل الحمدلله }

- $\beta^{+2, \text{ or } 3}$ homozygous = thalassemia intermedia stage 2
- Heterozygosity of β^0, or β^+ = thalassemia minor → stage 3
- Mild hypochromic, microcytic anemia
- Patients are usually asymptomatic with symptoms occurring under stressful conditions such as pregnancy.
- β thalassemia may also be found in combination with any of the hemoglobinopathies (S, C, or E) leading to a mild to severe anemia depending upon the particular combination.

α thalassemia

Alpha thalassemia manifested after birth immediately because alpha chains found in diffrent types of Hb including HbF .

-The disease is manifested immediately at birth
-There are normally four alpha chains, so there is a great variety in the severity of the disease.
- At birth there are excess γ chains and later there are excess β chains.
-These form stable, nonfunctional tetramers that precipitate leading to decreased RBC survival.

سبحان الله العظيم

- The disease is usually due to deletions of the α gene and occasionally to a functionally abnormal α gene.
- Since one gets two genes from each parent, **there are four types of α thalassemia**:
- Loss of ONE gene → silent carrier (-a/aa).
- Loss of TWO genes → thalassemia minor (trait) (-a/-a) or (--/aa) with mild anemia. → 20% of globin chains
- Loss of THREE genes → Hemoglobin H (--/-a) → accumulation of β chains → association of β chains in groups of 4 → Hb H (has a higher affinity for O2 and precipitates in older cells) → anemia may be chronic to moderate to severe.
- Loss of FOUR genes → Hemoglobin Barts (--/--) (NO α chains produced, only γ chains present → association of 4 γ chains → hydrops fetalis which is fatal with stillbirth or death within hours of birth.
- Hemoglobin Barts (γ_4) forms and has such a high affinity for O_2 that no O_2 is delivered to the tissues.
- Hb S/ α thalassemia: symptomless to moderate anemia

الحمدلله

Delta/beta (δ/β) thalassemia (Hereditary persistence of Hb F)

- Both δ and β chains are absent with no or little compensatory increase in γ chain synthesis. → one band of Hb F
- This leads to 100% Hb F and mild hypochromic, microcytic anemia
- Since Hb F has an increased affinity for O_2, this results in polycythemia.

↳not survive few years after birth

Hemoglobin Constant Spring

- Formed by a combination of two structurally abnormal α chains (each elongated by 31 amino acids at the COOH end) and two normal β chains. Prolongation of one chain = it will be unstable
- Homozygous individuals have mild hypochromic, microcytic anemia similar to a mild a α thalassemia.

Hemoglobin Lepore

- A normal α chain plus a δ-β hybrid (N-terminal δ, and C-terminal β). → هجين
- There is ineffective synthesis of the hybrid chain leading to α chain excess and the same problems seen in β thalassemia.
- Homozygous individuals have a mild to severe hypochromic, microcytic anemia
- Heterozygous individuals are asymptomatic.

حديث شريف 🌹😊

- في الحديث عن النبي صلى الله عليه وسلم: يقولُ اللَّهُ تَعالَى: أنا عِنْدَ ظَنِّ عَبْدِي بي، وأنا معهُ إذا ذَكَرَنِي، فإنْ ذَكَرَنِي في نَفْسِهِ ذَكَرْتُهُ في نَفْسِي، وإنْ ذَكَرَنِي في مَلَإٍ ذَكَرْتُهُ في مَلَإٍ خَيْرٍ منهمْ، وإنْ تَقَرَّبَ إلَيَّ بشِبْرٍ تَقَرَّبْتُ إلَيْهِ ذِراعًا، وإنْ تَقَرَّبَ إلَيَّ ذِراعًا تَقَرَّبْتُ إلَيْهِ باعًا، وإنْ أتانِي يَمْشِي أتَيْتُهُ هَرْوَلَةً.