Hemoglobinopathies

hemolytic anemia → ↓Pyruvate kinase enz
↓G6PD

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

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.

deletions, frame shift mutations, cross-over, and fusions of subunits.

- 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

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

Pathophysiology of the disease

- When oxygenated, Hb S is soluble, but when oxygen tension

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  decreases, Hb S in the deoxyhemoglobin state polymerize
  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".

- 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.

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- This, however, creates more deoxyhemoglobin, and hence, more sickling.

Clinical findings

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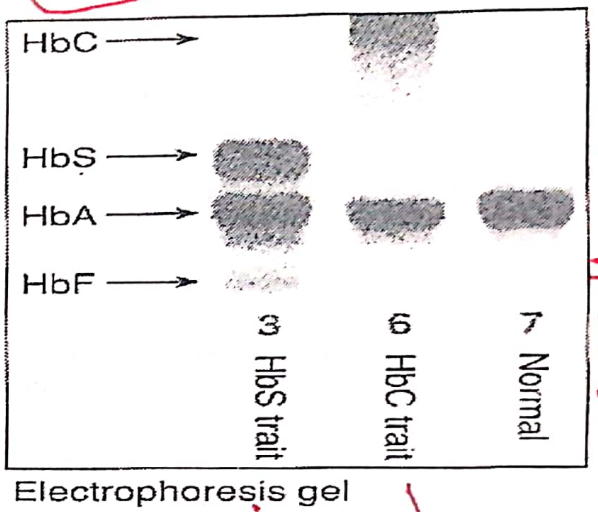
Clinical findings

-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

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



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

- 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

microcytic anemia
- Heterozygous individuals are asymptomatic.

Hbs/c/D is qualitative → يعني في قدرة وظيفية في العمل
but Thalassemia is quntitative types → تكون في وظيفة الجينات globin chain. خربانة ما بتعطي كمية كافية من

Hb m variants → خلل في هيموغلوبين ... it will not reduce met.Hb to Hb and this will stop function of Hb in carry O2

So mutation in gene encoding glyceraldehyde-3-phosphate dehydrogenase no production of NADH + H so met.Hb reductase ما رح يشتغل

1. genetic mutation of the gene encoding for met.Hb reductase enzyme
2. genetic mutation of the gene encoding for one the enzyme of glycolysis.

طيب اشي العلاقة يلي تربط ما بين الـ glycolysis والـ function of met. Hb reductase ??

انها تعطي providing NADH+H للانزيم / glyceraldehyde 3-phosphate dehydrogenase في glycolysis pathway NADH + H انزيم رقم (7)

fragility

- Heterozygous individuals are symptomless

HbS
HbC
HbC/S
HbD/S
HbE الاقل ظهور

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
- 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.

the β

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:

1. A mutation in the noncoding introns of the gene resulting in inefficient RNA splicing to produce mRNA, and therefore, decreased mRNA production → mRNA with intron which is nonfunctioning
2. The partial or total deletion of a globin gene → RNA polymerase → يجيب او لا يجيب promoter
3. A mutation in the promoter leading to decreased expression
4. A mutation at the termination site leading to production of longer, unstable mRNA
5. A nonsense mutation.

Types of thalassemia

- (gama) γ- thalassemia
- delta thalassemia
- Zeta thalassemia
- epsilon thalassemia

Zeta, epsilon gene switch on during 1st 6-weeks of gestation

globin chain defected

Any of these defects lead to:

- An excess of the other normal globin chain
- 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. 4-6 months
- 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. (homozygous)
  2. β^+ in which there is a partial block in β chain synthesis.

replaced by γ- α chains

- 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

β-thalassemia → 3-subclasses → major, intermediate, minor

-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. 10-50% Bet normal

β نقص
α كثير
- 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. → غير قادر ان ينتج BM normal Hb and normal R

- In circulating RBCs, α chains may also precipitate leading to pitting in the spleen. → basophilic stippling
- Untreated individuals die early, usually of cardiac failure (due to overwork and hemochromatosis). → due to hemolysis of erythrocyte

- 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

- 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 → homozygous

-Therapy: transfusions plus iron chelators to prevent hemochromatosis and tissue damage from iron overload

upon the particular combination.

α thalassemia

-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. replacement of substitution of α chain with γ chains → tetramers
-These form stable, nonfunctional tetramers that precipitate leading to decreased RBC survival.

-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). 75% of α chains are produced and that's enough
- Loss of TWO genes → thalassemia minor (trait) (-a/-a) or (--/aa) with mild anemia.
- 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 Beta no delta → No HbA2 no HbA → HF

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.
- 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.

Hemoglobin Constant Spring

due to mutation in termination site → so

- 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.

Carboxylic terminal end

- Homozygous individuals have mild hypochromic, microcytic anemia similar to a mild a α thalassemia.

Hemoglobin Lepore

[Subunit fusion] (mix

- A normal α chain plus a δ-β hybrid (N-terminal δ, and C-terminal β).
- 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.