Doctor.021

no. 4

HLS PATHOLOGY

Writer: Hala Ajlouni

Corrector: Jana Alhittawe

Doctor: Tariq Al adaily

HEMOGLOBINOPATHIES

THALASSEMIA

- **Group of inherited disorders that result in decreased production of either α/β chains.** (Group of diseases that share the decreased synthesis of Hb)
- **Amount of synthesized Hg is below normal**
- **The deficiency in one of globin chains (α/β) results in a relative increase in the other one, excessive unpaired chains will cause instability and hemolysis.** (If it was beta-Thalassemia for example >> deficiency in beta chains production>> relative increase in alpha chains>> unstable Hb >> Hemolysis).
- **Mode of inheritance: autosomal recessive**
- **Common in Middle East, Africa and Southeast Asia** (old world)
- **Resistant to infection by malaria falciparum.** (Phenomena in hemoglobinopathies that they have natural resistance for Malaria Falciparum).
- **Normal Hg types in adults:HgA** (most affected type by thalassemia since its composed of (α2/β2) **, HgA2, HgF** (least affected).

GENETICS

α-Thalassemia

- **α-chain is encoded by 2 genes on chromosome 16.** (2 genes on each chromosome>> we have two chromosomes >> we have 4 genes for α)
- **Most mutations in α-thalassemia are deletion.**
- **Deletion in 1,2 gene(s) results in a silent carrier.**(no symptoms, there's 2 more remaining chains, symptoms start to appear when 3,4 genes are deleted).
- **Deletion of 4 genes results in hydrops fetalis.** Incompatible with life, either die in utero or shortly after birth.
- **Deletion of 3 genes results in Hemoglobin H disease (extra β- chains binds each other to a tetramer called Hg-H, extra γ- chains form Hg-Barts). Both have high affinity to oxygen.** (Even with the high affinity for oxygen they cannot correct anemia).

β-Thalassemia

- **B-chain is encoded by a single gene of chromosome 11 (2 chromosomes= 2 genes)**
- **Most mutations in β-thal are point mutations. Different mutations between patients (variable severity ranging from being asymptomatic to having severe anemia)**
- **β0: no production of β-chain**
- **β+: decreased production of β-chain. Less than normal**
- **β/β+:silent carrier or mild anemia (thal-minor).One normal beta and the other has reduced amount ,patients have normal α with minor decrease in β chain(slow transcription/ translation).**
- **β+/β+: thalassemia intermedia.(Decreased production in both genes, symptoms start to appear).**
- **β0/β0 (no production at all) or β0/β+(very few amount of beta): thalassemia major (Cooley anemia). Severe anemia appears early in life.**
- **Extra α-chains remain uncoupled, causing hemolysis of RBCs in spleen and erythroid precursors in bone marrow (ineffective erythropoiesis).**

β-Thalassemia has more hemolysis than α-Thalassemia

β-Thal (low production of beta so alpha accumulates) >> tetra α>> insoluble in cytoplasm>> precipitates >> lysis of erythroid cells in bone marrow ,and RBCs in blood are destroyed by the spleen.

In α-Thalassemia>> tetra beta>> well soluble>> no severe hemolysis.

Morphology

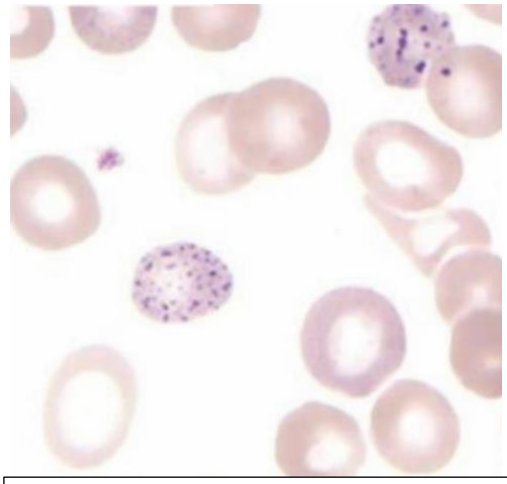
- **Hypochromic microcytic anemia. Because of the decreased amounts of Hb cells gets smaller and more pale.**
- **Target cells. central redness in RBCs.**

Target cells are seen in cases that have abnormal Hb (iron deficiency, thalassemia, sickle cell anemia).

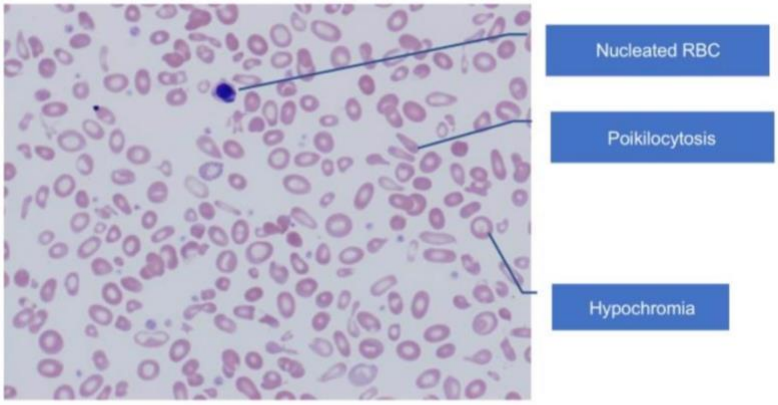
- **Basophilic stippling (ribosomes) (basophilic=blue, stippling= small dots)**
- **In thalassemia major:**
- **Peripheral blood: + poikelocytosis (abnormal shapes), nucleated RBCs (high erythropoietin>> activates BM>> more nucleated RBCs (immature cells).**

▪ **Bone marrow: ↑↑ normoblasts, filling BM spaces and expanding into bone, hemosiderosis (deposition of high amounts of iron in BM and tissues).**

Normoblasts (nucleated RBCs, but they're not effective in controlling anemia because they undergo hemolysis).



Basophilic stippling



THALASSEMIA MAJOR BLOOD FILM

Clinical Symptoms

▪ **Thalassemia traits (carriers) are asymptomatic, normal life span, premarital test is important (if both of them are carriers= increased chance for offsprings to have Thalassemia major)**

▪**Thalassemia major: symptoms begin after age of 6 months(when switch from HbF to HbA occur, before switching HbF has no beta chains so patients are not affected until it shifts to HbA at the age of 6 months), persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion. (Thal-major patients depend on blood transfusion)**

▪ **Systemic hemochromatosis and related organ damage occurs in 2nd or 3rd decade of life. They are given chelating agents as a treatment as they bind iron).**

▪**Thalassemia intermedia (in β-Thalassemia) and HgH(in α-thalassemia) disease have moderate anemia, do not require regular blood transfusion (mild symptoms).**

Diagnosis

- **Hemoglobin electrophoresis test (definite diagnosis, This device breaks RBCs and test extracted Hb by measuring the amount of each Hb type).**
- **In all types of β-thal, there is increase in HgA2 and HgF percentages (because HbA synthesis is reduced so there is a relative increase in other types)**
- **In β-thal major, HgA is absent or markedly decreased**
- **In HgH disease, HgH and Hg Barts bands appear**
- **In α-thal carrier and minor, no abnormality is found (hard to test by Hb electrophoresis). Genetic testing is available (DNA testing).**

SICKLE CELL ANEMIA

- **Most common familial hemolytic anemia worldwide (inherited disease).**
- **Common in Africa, Middle East, Saudi Arabia (old world) , African Americans (western countries).**
- **Resistant to malaria falciparum infection**
- **Autosomal recessive**
- **Caused by single amino acid substitution (point mutation)**

(glutamic acid→valine) in β-chain.Glutamic acid is hydrophilic when it is substituted by valine which is hydrophobic, there is a change in characteristics of the β-chain.

- **In sickle cell disease (homozygous) both β genes are mutated, Hg electrophoresis shows HgS and absent HgA**
- **In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA and HgS band.**

Pathogenesis

- **In deoxygentated case, HgS tends to polymerize in a longitudinal pattern, distorting cell shape and creating sickle shape.**
- **The change is reversible by re-oxygenation, however, with repeated sicklings, cell membrane is damaged and the RBC is shrunken permanently with a sickle shape.**

In deoxygenated state (T-state) HbS tends to polymerize and arrange in a longitudinal pattern, it becomes elongated and curved creating sickle shape

and that's why it's called sickle cell disease.This change is reversible initially when switching back to the oxygenated state (R state), with repeated sicklings cell membrane is damaged and fluids leak so RBCs shrunk and sickling becomes irreversible.

▪The presence of normal HgA (carrier) and increased HgF (newborn) inhibits HgS polymerization.

For sickling to happen, 2 genes must be mutated (homozygous HbS)>> being heterozygous (carriers) prevents sickling. Also HbF (newborns) has no beta chain where the mutation occur,so that prevents sickling to happen until the age of 6 months when switching to HbA occurs).

▪Increased HgS concentration inside RBC promotes sickling (dehydration, acidosis), while decreased HgS concentration prevents sickling (the presence of additional α-thalassemia).

Patients with α-thalassemia combined with HbS >> have less hemolysis than homogenous HbS,why?

HbS is made up of 2 alpha chains and two abnormal beta (S chains)>> α-thalassemia means low production of alpha>> so alpha is not available to produce HbS>> decreased amounts of HbS.

▪Sickle-shaped RBCs take a longer time to pass through capillaries, non deformable. Do not squeez to fit in capillaries so they longer time to pass

▪Removed by macrophages in spleen (extravascular hemolysis)

▪Also adhere to endothelial cells, may create a thrombus. (Fatal part)

Clinical features

▪ Chronic moderate-severe hemolytic anemia, manifesting after the age of 6-months (dependent on fraction of sickled cells). The chronic course is interrupted by repeated sudden attacks of worsening anemia.

They already have persistence anemia but with worsening attacks.

▪Vaso-occlusive crisis (independent on fraction of sickled cells>> can happen at any percentage), results in organ infarction. Commonly associated with systemic infection, inflammation, dehydration and acidosis.

Vaso-occlusive crisis (occlusion of capillaries and arterioles (thrombosis) can affect any organ)

▪**Hand-foot syndrome (ischemia in digits (very painful), digits may become shorter than normal), acute chest syndrome (infarction of lung,MI (severe pain) >> they can't breath>> more hypoxia), stroke, myocardial infarction, retinopathy, autosplenectomy (infarction of the spleen, hemolysis in spleen like any hemolytic anemia, but with aging spleen becomes infarcted and fibrotic, then disappears without any surgery).**

▪**Aplastic-crisis (BM infarction ,BM doesn't produce any cell): infection by Parvovirus B19, causing worsening anemia, self-limited.**

B19 virus targets normoblasts (nucleated RBCs) in BM, in healthy adults infected people are not affected. But in Thal,sickle cell,Hemolytic anemia >> they have tendency for this virus >> worsening of anemia.

Remember: worsening in sickle cell anemia happens as a result of the repeated attack for 2 reasons:

Aplastic crisis.

B19 virus infection.

▪ **Susceptibility for encapsulated bacteria (pneumococcus, salmonella).**

They used to take prophylactic antibiotic for the rest of their lives but now they have specific vaccines (because spleen is removed)

▪ **Sickle cell carrier: asymptomatic.**

Laboratory Findings

▪**Routine blood smear: presence of sickle cells, target cells**

▪**Sickling test: adding hypoxic agent to RBCs promote sickling**

When there is no enough cell to diagnose

▪**Hemoglobin electrophoresis (definite test >> shows if the patient is a carrier or diseased).**

▪**In sickle cell trait,Blood smear is normal.**