HEMOGLOBINOPATHIES

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THALASSEMIA

- Group of inherited disorders that result in decreased production of either α/β chains Decreased production oh HGA
- Amount of synthesized Hg is below normal
- The deficiency in one of globin chains results in a relative increase in the other one, excessive unpaired chains will cause instability and hemolysis
- Mode of inheritance: autosomal recessive So there are salient carriers
- Common in Middle East, Africa and South East Asia (Old world countries)
- Resistant to infection by malaria falciparum Patient has thalassemia
- Normal Hg types in adults: HgA, HgA2, HgF

(most affected type by thalassemia since it's composed of (α2/β2)

If it was beta-Thalassemia for example >> deficiency in beta chains production>> relative increase in alpha chains>> unstable Hb >> Hemolysis)

GENETICS

- 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

While in beta the mutation is point mutation

- Deletion in 1,2 gene(s) results in a silent carrier Thalessemia minor
- Deletion of 4 genes results in hydrops fetalis They die in uterus 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

Here we have a chains but less than beta result in Hg H when we have extra beta chains and Hg Bart's when we have extra y

In this disease we have HgA but less than normal

GENETICS

- B-chain is encoded by a single gene of chromosome 11
- Most mutations in β-thal are point mutations
- β^0: no production of β-chain
- β^+: decreased production of β-chain
- β/β^+:silent carrier or mild anemia (thal-minor)
- β^+/β^+: thalassemia intermedia
- β^0/β^0 or β^0/β^+: thalassemia major (Cooley anemia)
- Extra α-chains remain uncoupled, causing hemolysis of RBCs in spleen and erythroid precursors in bone marrow (ineffective erythropoiesis)

In total we have 2 genes

Less than normal

One gene is normal

The symptoms is worse than a

Both genes are not functioning or one is not functioning and the another produce little amount

The extra a chains are not soluble

MORPHOLOGY

- Hypochromic microcytic anemia
- Target cells central redness in RBCs.

Not specific for thalassemia, we will see them in the sickle

- Basophilic stippling (ribosomes) (basophilic=blue, stippling= small dots)

Small dots all over the cells and those dots are residual ribosomes

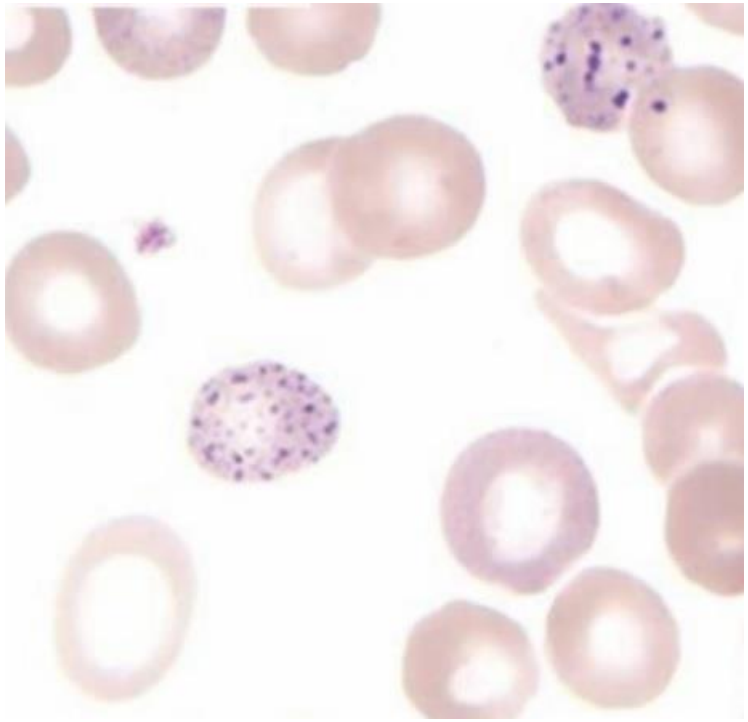
- In thalassemia major:
- Peripheral blood: + poikelocytosis, nucleated RBC s Not mature
- Bone marrow: ↑↑ normoblasts, filling BM spaces and expanding into bone, hemosiderosis (Hemochromatosis)

As a result of iron deposition

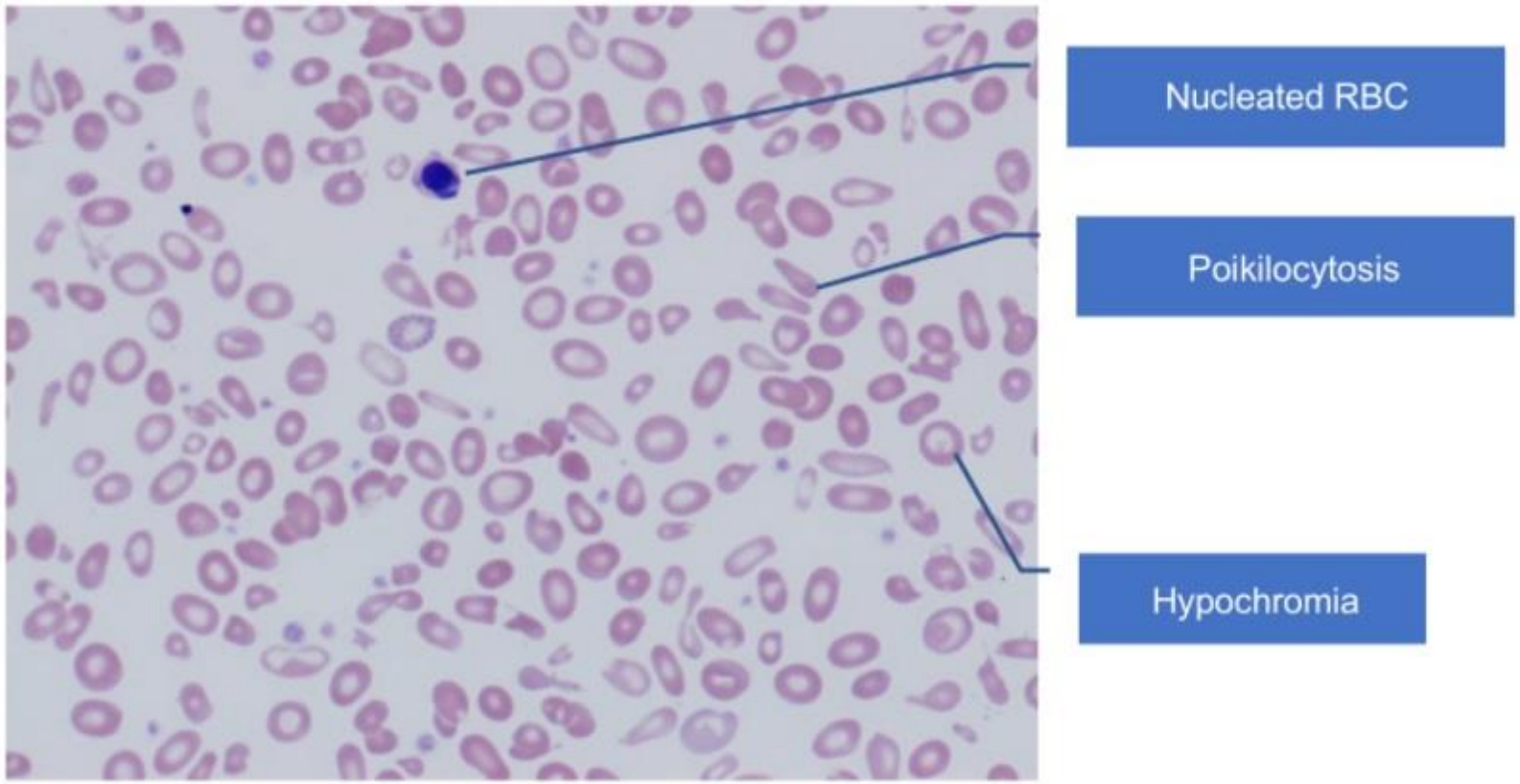
The iron will increase as a result of 2 things :

1-regular blood transfusions

2-the increase of erythropoietin will inhibit the hepcidine (hepcidine inhibits the absorption of iron)



BASOPHILIC STIPPLING OF RBCS



THALASSEMIA MAJOR BLOOD FILM

CLINICAL SYMPTOMS

Minor

- Thalassemia traits are asymptomatic, normal life span, Incidentally finding premarital test is important مهمة بفحص ما قبل الزواج حتى ما يتم توريث المرض للأبناء
- Thalassemia major: symptoms begin after age of 6 months, persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion They have splenomegaly and hepatomegaly

The treatment is regular blood transfusion

- Systemic hemochromatosis and related organ damage occurs in 2nd or 3rd decade of life

Late and fatal complication

In beta

In alpha

- Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion

But life long anemia

DIAGNOSIS

How to distinguish if it thalassemia alpha or beta ?

By second test called:

- Hemoglobin electrophoresis test
- In all types of β-thal, there is increase in HgA2 and HgF percentages Cuz those patients have excess alpha
- In β-thal major, HgA is absent or markedly decreased We can see HgF
- In HgH disease, HgH and Hg Barts bands appear
- In α-thal carrier and minor, no abnormality is found. Genetic testing is available

Cuz in the carriers there are a decreased synthesis of a, but the percentage is constant

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SICKLE CELL ANEMIA

- Most common familial hemolytic anemia worldwide
- Common in Africa, Middle East, Saudi Arabia, African Americans
- Resistant to malaria falciparum infection As in thalassemia
- Mode of inheritance: autosomal co-dominance
- Caused by single amino acid substitution (glutamic acid → valine) in β-chain Point mutation
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS and absent HgA Here both beta chains convert to sickle
- In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA and HgS bands

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

So when they reach the spleen they will be destroyed

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

They don't develop any sickling

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

PATHOGENESIS

- Sickle-shaped RBCs take a longer time to pass through capillaries, non deformable
- Removed by macrophages in spleen (extravascular hemolysis)
- Also adhere to endothelial cells, may create a thrombus

So the patients die early

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
- Vaso-occlusive crisis (independent on fraction of sickled cells), results in organ infarction. Commonly associated with systemic infection, inflammation, dehydration and acidosis.
- Hand-foot syndrome, acute chest syndrome, stroke, myocardial infarction, retinopathy, autosplenectomy
- Aplastic-crisis: infection by Parvovirus B19, causing worsening anemia, self-limited
- Susceptibility for encapsulated bacteria (pneumococcus, salmonella)
- Sickle cell carrier: asymptomatic

As a result of the triggers that promote the sickling of the cells

Another complication (Thrombus)

Examples:

Severe chest pain

Fatal

Ischemia for the bones of digits

Targets the normoblast

BM infarction ,BM doesn't produce any cell

Cuz of removal of spleen in autosplenoactomy

Autosplenoctomy (infarction of the spleen, hemolysis in spleen like any hemolytic anemia, but with aging spleen becomes infarcted and fibrotic, then disappears without any surgery)

LABORATORY FINDINGS

- Routine blood smear: presence of sickle cells, target cells

Curved cells

- Sickling test: adding hypoxic agent to RBCs promote sickling

to be sure التيست هاد بعمل قليلة cells ال كمية تكون لما

- Hemoglobin electrophoresis
- In sickle cell trait,

Blood smear is normal