HEMOGLOBINOPATHIES

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THALASSEMIA

- Group of inherited disorders that result in decreased production of either α/β chains
- 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
- Common in Middle East, Africa and South East Asia
- Resistant to infection by malaria falciparum
- Normal Hg types in adults: HgA, HgA2, HgF

GENETICS

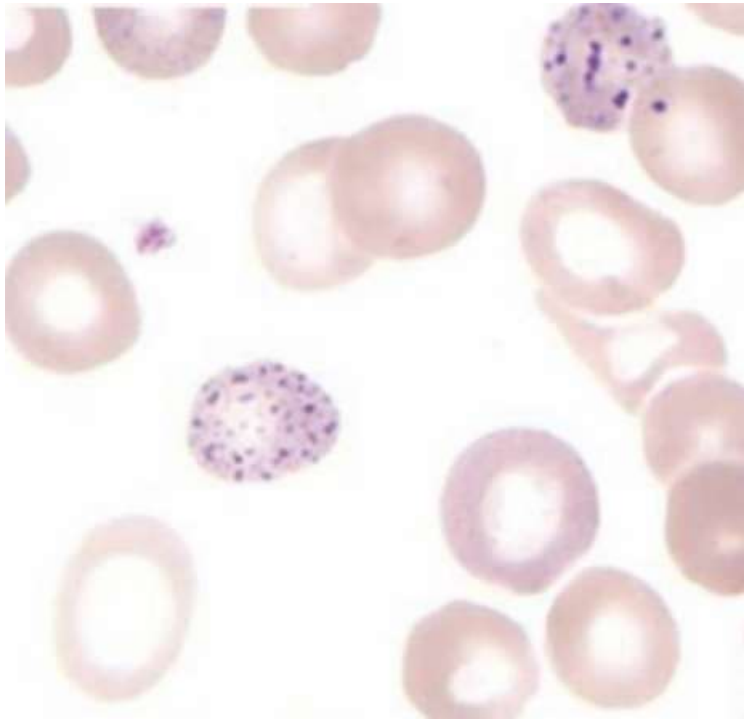
- α-chain is encoded by 2 genes on chromosome 16
- Most mutations in α-thalassemia are deletion
- Deletion in 1,2 gene(s) results in a silent carrier
- Deletion of 4 genes results in hydrops fetalis
- Deletion of 3 genes results in Hemoglobin H disease (extra β-chains binds each other to a tetramer called Hg-H, extra γ-chains form Hg-Barts). Both have high affinity to oxygen

GENETICS

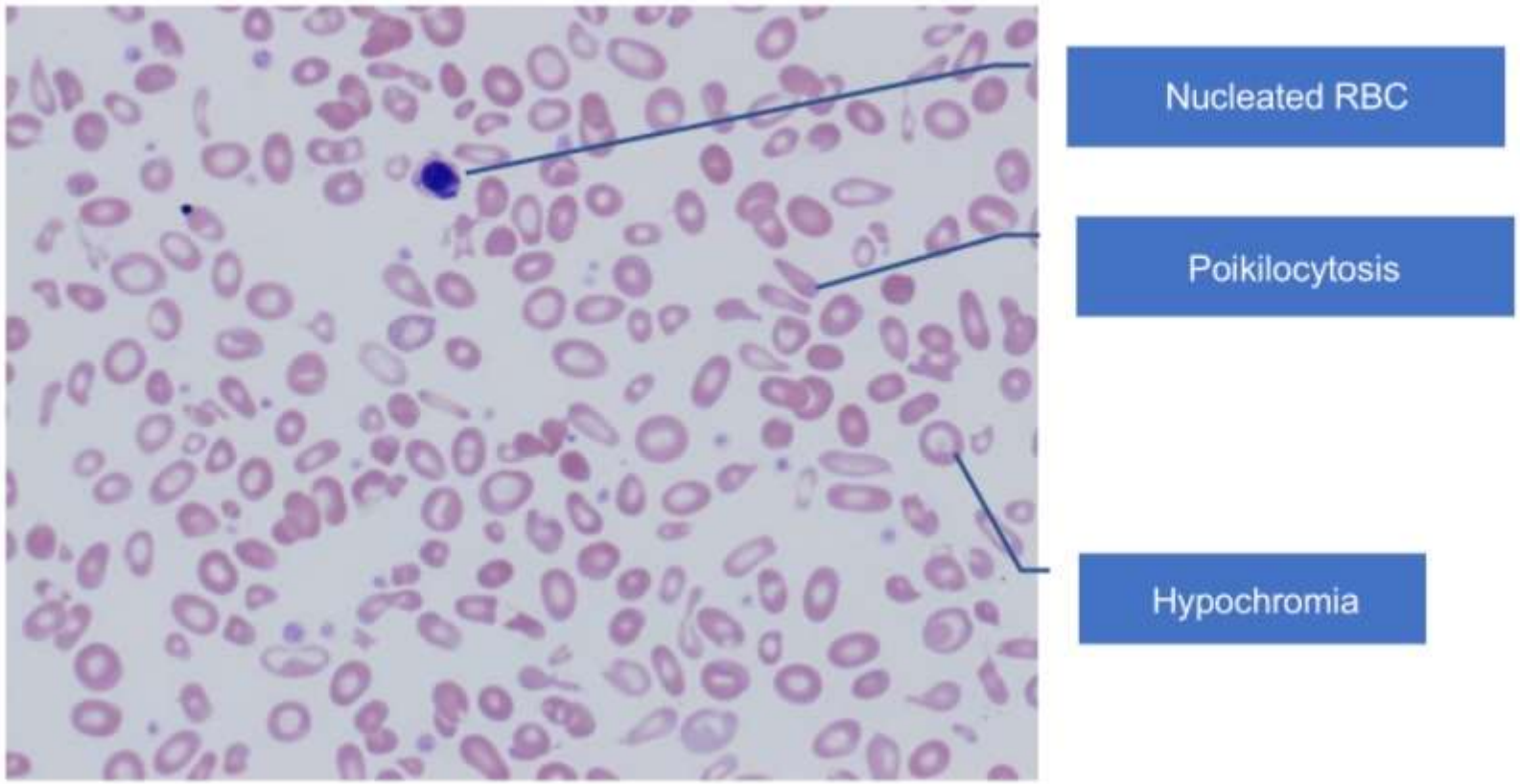
- B-chain is encoded by a single gene of chromosome 11
- Most mutations in β-thal are point mutations
- β^0: no production of β-chain
- β^+: decreased production of β-chain
- β/β^+:silent carrier or mild anemia (thal-minor)
- β^+/β^+: thalassemia intermedia
- β^0/β^0 or β^0/β^+: thalassemia major (Cooley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

MORPHOLOGY

- Hypochromic microcytic anemia
- Target cells
- Basophilic stippling (ribosomes)
- In thalassemia major:
- Peripheral blood: + poikelocytosis, nucleated RBC s
- Bone marrow: ↑↑ normoblasts, filling BM spaces and expanding into bone, hemosiderosis



BASOPHILIC STIPPLING OF RBCS



THALASSEMIA MAJOR BLOOD FILM

CLINICAL SYMPTOMS

- Thalassemia traits are asymptomatic, normal life span, premarital test is important
- Thalassemia major: symptoms begin after age of 6 months, persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion
- Systemic hemochromatosis and related organ damage occurs in 2nd or 3rd decade of life
- Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion

DIAGNOSIS

- Hemoglobin electrophoresis test
- In all types of β-thal, there is increase in HgA2 and HgF percentages
- 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. Genetic testing is available

SICKLE CELL ANEMIA

- Most common familial hemolytic anemia worldwide
- Common in Africa, Middle East, Saudi Arabia, African Americans
- Resistant to malaria falciparum infection
- Mode of inheritance: autosomal co-dominance
- Caused by single amino acid substitution (glutamic acid → valine) in β-chain
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS and absent HgA
- 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
- The presence of normal HgA (carrier) and increased HgF (newborn) inhibits HgS polymerization
- 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

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

LABORATORY FINDINGS

- Routine blood smear: presence of sickle cells, target cells
- Sickling test: adding hypoxic agent to RBCs promote sickling
- Hemoglobin electrophoresis
- In sickle cell trait,

Blood smear is normal