Thalassemia, Sickle Cell Disease's summary

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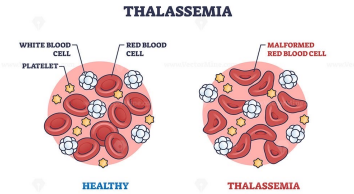
THALASSEMIA

Group of inherited disorders that result in decreased production of either α/β chains

decrease in : α chain > α thalassemia

decrease in : β chain > β thalassemia

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 (most affected one) , HgA2 (important in diagnosis) , HgF

GENETICS

α-thalassemia

🧬α-chain is encoded by 2 genes on chromosome 16 , so the total is 4 genes "2 maternal and 2 paternal"

🧬Most mutations in α-thalassemia are deletion

🧬Deletion in 1,2 gene(s) : results in a silent
carrier or very minor symptoms

🧬Deletion of 4 genes : results in hydrops fetalis (dies 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 "consists of 4 β- chains" , extra γ- chains form Hg-Barts "consists of 4 γ- chains"). Both have high affinity to oxygen (these patients have long life anemia but they are commetable with life)

β-thalassemia

🧬B-chain is encoded by a single gene of chromosome 11 , so the total is 2 genes "1 maternal and 1 paternal"

🧬Most mutations in β-thal are point mutations

🧬β0 : no production of β-chain

🧬β+ : decreased production of β-chain

🧬β/β+ : silent carrier or mild anemia (thalassemia minor)

🧬β+/β+ : thalassemia intermedia

🧬β0/β0 or β0/β+ : thalassemia major (Cooley anemia)

🧬Extra α-chains remain uncoupled, causing hemolysis of RBCs
in spleen and erythroid precursors in bone marrow
(ineffective erythropoiesis)

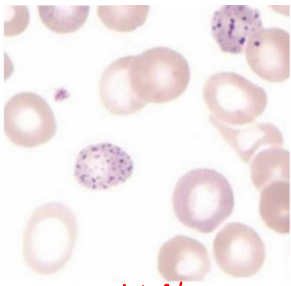
MORPHOLOGY :

- Hypochromic microcytic anemia (we have low amount of Hb so it's like IDA)
- Target cells
- Basophilic stippling (small blue dots) (Ribosomes)

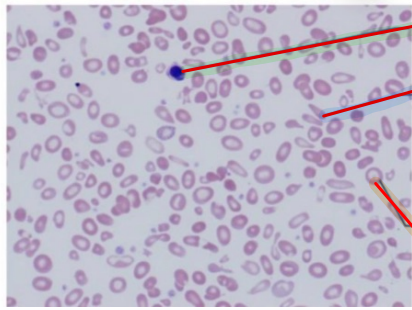
In thalassemia major:

- Peripheral blood : + poikelocytosis, nucleated RBC's
- Bone marrow: ↑↑ normoblasts (because of erythropoietin effect) , filling BM spaces and expanding into bone (steal O2 from bone so patient can have abnormal bone growth) , hemosiderosis (major problem of thalassemia major , hemolysis will get iron out and the increased erythropoietin which works as an antagonist to hepcidin will decrease it and there will be no inhibition for iron absorption and this will result in hemosiderosis)

Treatment :blood transfusion , we can't correct anemia because it's inherited



Basophilic stippling of RBCs



Thalassemia major blood smear

CLINICAL SYMPTOMS :

- Thalassemia traits are asymptomatic (you can detect the abnormality if you do complete blood count test > hypochromic microcytic "but in mild degrees"), normal life span, premarital test is important
- Thalassemia major : symptoms begin after age of 6 months (because till 6 months we still have HbF which can makes Hb function) , persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion
- Systemic hemochromatosis and related organ damage (can affects heart , endocrine, ,...) occurs in 2nd or 3rd decade of life , and at this time patient will die
- Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion

DIAGNOSIS :

- Hemoglobin electrophoresis test (separate chains and gives percentage of each chain) - 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

Table comparing

Alpha & Beta thalassemia

Characteristics	Alpha thalassemia	Beta thalassemia
Definition	Reduced formation of alpha polypeptide chains	Reduced formation of beta polypeptide chains
Symptoms	None or small red blood cells, hemolytic anemia, paleness, fatigue, jaundice, enlarged spleen	None or hemolytic anemia, paleness, fatigue, jaundice, gallstones, and enlarged spleen
Diagnosis	Smaller than usual red blood cells, genetic testing	Hemolytic anemia, genetic testing, high fetal hemoglobin and hemoglobin A_2 or lower than normal overall hemoglobin
Causes	Genetic mutation of alpha genes on chromosome 16	Genetic mutation of beta globin genes on chromosome 11
Fetal mortality	In homozygous condition Bart's hydrops fetalis occurs and the fetus dies in utero	In homozygous condition fetus survives in the uterus because there is fetal hemoglobin, but the child will have severe complications later

SICKLE CELL ANEMIA :

Most common familial hemolytic anemia worldwide (more common than thalassemia)

- Common in Africa, Middle East, Saudi Arabia, African Americans
- Resistant to malaria falciparum infection (same as thalassemia)
- Autosomal recessive

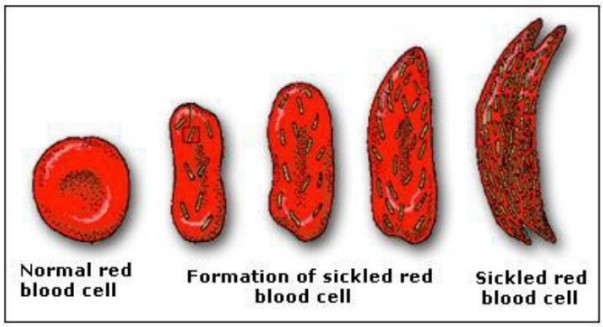
- Caused by single amino acid substitution (glutamic acid "hydrophilic" → valine "hydrophobic") in β- chain
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS and absent HgA
- In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA and HgS bands

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 with repeating sickling , cell membrane is damaged and RBCs will be shrunken and take a sickle shape .

- The presence of normal HgA (carrier "they don't have any symptoms because they don't have sickling or hemolysis") and increased HgF (newborn) inhibits HgS polymerization (we can use HbF as a treatment by giving drugs that increase HbF)

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



CLINICAL SYMPTOMS :

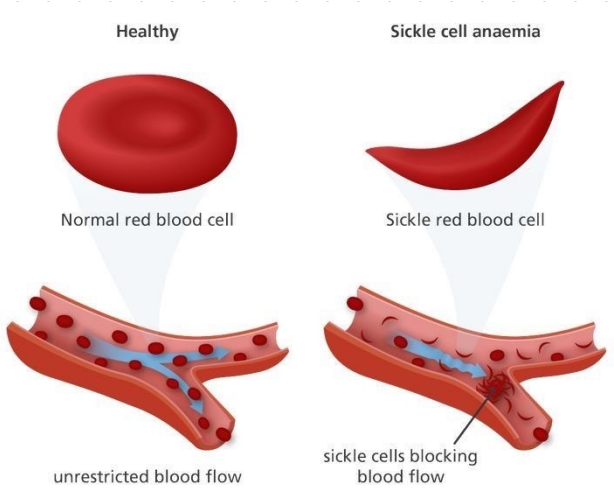
- Sickle-shaped RBCs take a longer time to pass through capillaries
- Removed by macrophages in spleen (extravascular hemolysis)
- Also adhere to endothelial cells, may create a thrombus
- Chronic moderate-severe hemolytic anemia, manifesting after the age of 6-months (dependent on fraction of sickled 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 : secondary to bone infraction by Vaso-occlusive crisis or to infection by Parvovirus B19, causing worsening anemia, self-limited
- Susceptibility for encapsulated bacteria (pneumococcus , salmonella) , as a result of auto splenectomy

- Sickle cell carrier:asymptomatic
- Routine blood smear: presence of sickle cells, target cells

DIAGNOSIS :

- Sickling test: adding hypoxic agent to RBCs promote sickling , in normal individuals they don't sickle
- Hemoglobin electrophoresis
- DNA testing

In sickle cell trait, Blood smear is normal



Thalassemia/ past papers questions :

Hb Bart means that you have:
a) 4 chains of gamma
b) 4 chains of beta
c) 3 chains of beta and 1 chain of alpha.

A

HbH is caused by:
a) Deletion of 3 genes
b) Deletion of 4 genes
c) Mutation in 3 genes
d) Mutation in 4 genes

A

A 2-year-old boy is brought to the clinician by his parents due to easy fatigability and growth delay. He is at the 30th percentile for length and below the 10th percentile for weight. Hematological tests and hemoglobin electrophoresis are obtained Hb : 10.8 , high HbA2 , absent HbA1 , Which of the following is the most likely diagnosis?
A- α-thalassemia major
B- β-thalassemia minor
C- Sickle cell disease
D- Hemoglobin H disease
E- β-thalassemia major
F- Sickle cell trait

E

SICKLE CELL ANEMIA / past papers questions :

Doesn't worsen sickle cell trait:
a) Malarial infection
b) Hypoxia
c) Dehydration
d) Acidosis

A

Glutamic acid to valine (at position 6) is an amino acid substitution seen in the ---------- chain in sickle-cell disease.
A-alpha chain
B- beta chain
C- delta chain

B

Newborns that have sickle-cell disease are initially asymptomatic because ---------- levels are high, while hemoglobin S levels are low.
A- hemoglobin minor
B- hemoglobin C
C-hemoglobin F
D-hemoglobin y

C