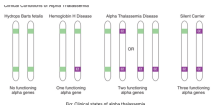
Thalassemia Overview

Thalassemia is a group of inherited blood disorders characterized by reduced production of either the α or β globin chains, leading to decreased hemoglobin synthesis and subsequent anemia. The imbalance between globin chains results in unpaired, excessive chains that cause instability in red blood cells (RBCs), leading to hemolysis.

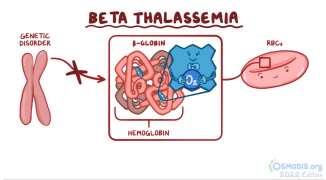
Genetics

Thalassemia follows an autosomal recessive mode of inheritance and is most prevalent in regions such as the Middle East, Africa, and Southeast Asia. The disease also provides a degree of resistance against Plasmodium falciparum, the parasite responsible for malaria.

1. Normal Hemoglobin Types in adults include Hemoglobin A (HgA), Hemoglobin A2 (HgA2), and Hemoglobin F (HgF).
2. α-Thalassemia:
   - The α-chain is encoded by two genes on chromosome 16.
   - Most α-thalassemia mutations are gene deletions.
   - Deletion of one or two genes results in a silent carrier state, while deletion of all four genes leads to hydrops fetalis (fatal condition).
   - Deletion of three genes causes Hemoglobin H (HgH) disease, where excessive β chains form tetramers (HgH), and γ chains form Hg-Barts, both of which have high oxygen affinity.

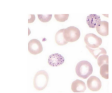


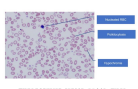
3. β-Thalassemia:
   - The β-chain is encoded by a single gene on chromosome 11.
   - Most β-thalassemia mutations are point mutations.
   - Severity depends on whether mutations completely stop β-chain production (β0) or only reduce it (β+).
     - β/β+ results in a silent carrier or mild anemia (thalassemia minor).
     - β+/β+ causes thalassemia intermedia.
     - β0/β0 or β0/β+ results in thalassemia major (Cooley's anemia).



Pathophysiology

- The imbalance between globin chains causes hemolysis of red blood cells, particularly in the spleen. This also leads to ineffective erythropoiesis (defective red blood cell production) in the bone marrow, contributing to hypochromic microcytic anemia and the appearance of target cells and basophilic stippling (due to ribosome aggregates) in blood smears.
- In thalassemia major, additional findings include:
  - Peripheral Blood: Poikilocytosis (abnormal shapes of RBCs) and nucleated RBCs.
  - Bone Marrow: Hyperactive normoblast production, filling bone marrow spaces and causing bone deformities.


BASOPHILIC STIPPLING OF RBCS


THALASSEMIA MAJOR BLOOD FILM

Clinical Manifestations

- Thalassemia Traits (carriers of the disease) are asymptomatic and have a normal lifespan. Premarital genetic testing is essential to detect carriers.
- Thalassemia Major: Symptoms usually appear after six months of age, as fetal hemoglobin (HgF) starts to decrease. These include:
  - Persistent anemia
  - Growth retardation
  - Skeletal abnormalities
  - Regular blood transfusions help manage symptoms.
- Thalassemia Intermedia and Hemoglobin H Disease: These cause moderate anemia but usually do not require regular transfusions.

Complications

In thalassemia major, iron overload (hemochromatosis) from regular blood transfusions can cause organ damage in the second or third decade of life.

Diagnosis

1. Blood Smears: Hypochromic microcytic anemia, basophilic stippling, target cells,
2. Hemoglobin Electrophoresis:
   - All forms of β-thalassemia show increased levels of HgA2 and HgF.
   - In β-thalassemia major, HgA is absent or significantly reduced.
   - In Hemoglobin H disease, HgH and Hg-Barts bands are visible.
   - In α-thalassemia carriers and minors, there are no abnormalities, but genetic testing is available for confirmation.

Sickle Cell Anemia Overview

Sickle cell anemia is the most common familial hemolytic anemia worldwide, primarily affecting populations in Africa, the Middle East, Saudi Arabia, and African Americans. It provides resistance to Plasmodium falciparum malaria. The condition follows an autosomal recessive inheritance pattern and is caused by a single amino acid substitution (glutamic acid → valine) in the β-globin chain of hemoglobin (Hg), which leads to the production of hemoglobin S (HgS).

Genetics

1. Inheritance:
   - Sickle Cell Disease: Homozygous for HgS, leading to severe symptoms. Hemoglobin electrophoresis shows only HgS with absent HgA.
   - Sickle Cell Trait: Heterozygous, carriers have both HgA and HgS bands on electrophoresis but are usually asymptomatic.

Pathogenesis

In deoxygenated conditions, HgS tends to polymerize into long strands, distorting red blood cells (RBCs) into a sickle shape. Initially, the sickling is reversible with re-oxygenation, but repeated sickling damages the RBC membrane, making the sickle shape permanent.

Several factors influence sickling:

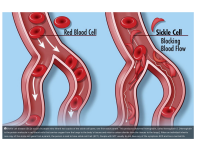
- Increased HgS concentration (e.g., dehydration, acidosis) promotes sickling.
- Decreased HgS concentration (e.g., presence of normal HgA or increased HgF) inhibits sickling.

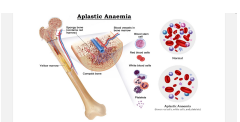
RBC Deformability and Hemolysis

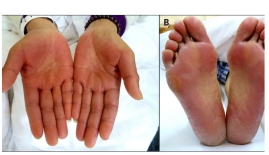
Sickled RBCs are less deformable and take longer to pass through capillaries, making them prone to destruction by macrophages in the spleen (extravascular hemolysis). These cells can also adhere to endothelial cells, leading to thrombus formation and vaso-occlusion.

Clinical Features

1. Chronic Hemolytic Anemia:
   - Moderate to severe, manifesting after six months of age as fetal hemoglobin (HgF) declines.
   - The chronic anemia is punctuated by acute episodes of worsening, called crises.
2. Vaso-occlusive Crisis:
   - Independent of the percentage of sickled cells, this crisis results in organ infarctions (e.g., stroke, myocardial infarction, acute chest syndrome).
   - Often triggered by infections, dehydration, inflammation, or acidosis.
3. Aplastic Crisis:
   - Typically caused by infection with Parvovirus B19, leading to worsened anemia that is self-limited.
4. Complications:
   - Hand-foot syndrome, retinopathy, autosplenectomy, increased susceptibility to encapsulated bacterial infections (e.g., Streptococcus pneumoniae).
5. Sickle Cell Trait:
   - Asymptomatic and usually discovered through screening.







Hand-Foot Syndrome (HFS) a.k.a. Palmar-Plantar Erythrodysesthesia (PPE)

Laboratory Findings

1. Routine Blood Smear:
   - Presence of sickle cells and target cells.
2. Sickling Test:
   - Exposing RBCs to a hypoxic agent induces sickling in those with sickle cell disease.
3. Hemoglobin Electrophoresis:
   - In sickle cell disease, only HgS is detected.
   - In sickle cell trait, both HgA and HgS are present, with normal blood smear findings.

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