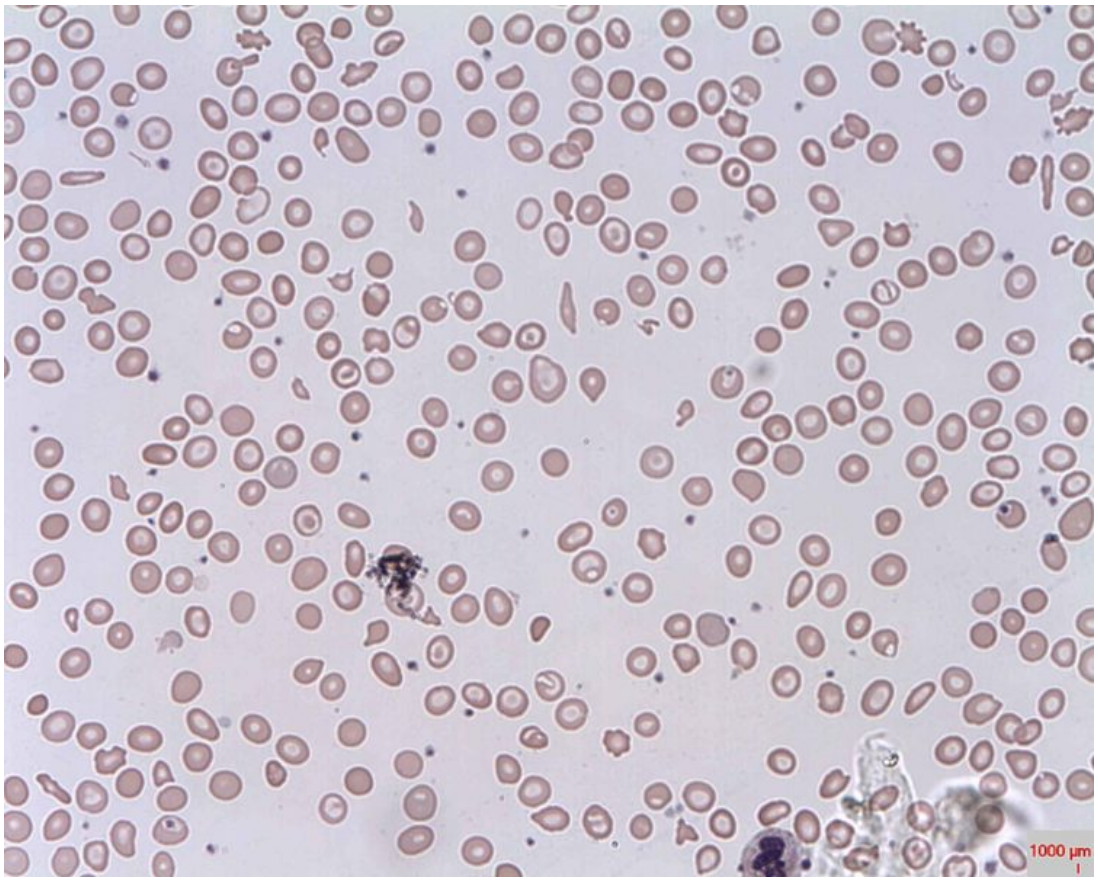
Thalassemia

See online here



Thalassemia is a hereditary cause of microcytic, hypochromic anemia. It is a deficiency in either the alpha (α) or beta (β) globin chain resulting in hemoglobinopathy. The presentation of thalassemia depends on the number of defective chains present. The consequent hemolysis results in severe systemic symptoms rendering the patient to be transfusion dependent.

Epidemiology and Etiology

Epidemiology

- Worldwide prevalence
- Mediterranean anemia, ~10% prevalence in the region (malaria-endemic areas)
- Carrier rate worldwide:
    - β- thalassemia: 3%
    - α- thalassemia: 5%
- α – presents in utero/from birth

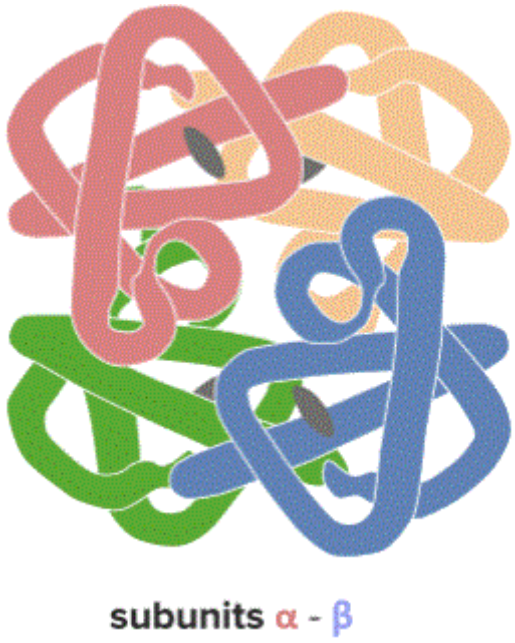


Image: “Thalassemia” by Lecturio.

- β – presents in infants around 6 months of age
- Equal incidence between the genders

Etiology

- Autosomal recessive
- **α-thalassemia**: 2 α – genes (HBA1 and HBA2) = 4 alleles (αα/αα)
    - Chromosome **16**
    - Deletion error
    - 4 types of disease variations
- **β-thalassemia:** 1 β-gene (HBB) = 2 alleles
    - chromosome **11**
    - Splicing mutation (β^+: decreased expression)
    - Nonsense mutation (β: absent expression)
    - Thalassemia minor: heterozygous, ~50% decreased synthesis
    - Thalassemia major: homozygous, no production of β-globulin, increase in HbA($\alpha_2\delta_2$) and HbF($\alpha_2\gamma_2$), no HbA

α- thalassemia		
Number of genes deleted/Genotype	**Disease**	**Outcome**
1 (αα/α-)	α-thalassemia minima	Silent carrier
2 (α-/α-; trans: African) (αα/–; cis: Asians)	α-thalassemia minor	Trait Mild anemia Cis: worsens with generations
3 (α-/–)	HbH disease (4β-chains)	Moderate to severe anemia
4 (–/–)	Hb Barts (4γ- chains)	Hydrops fetalis (incompatible with life)
β- thalassemia		
β/β or β^+/β	Thalassemia minor	Asymptomatic (mild)
β/β or β^+/β^+	Thalassemia intermedia	Occasional transfusion

β/β or β^+/β^+	Thalassemia major (Cooley anemia)	Transfusion-dependent

Video Gallery

Pediatric Thalassemia by Brian Alverson, MD
Alpha Thalassemia: Etiology by Carlo Raj, MD
Beta Thalassemia: Etiology and Pathogenesis by Carlo Raj, MD

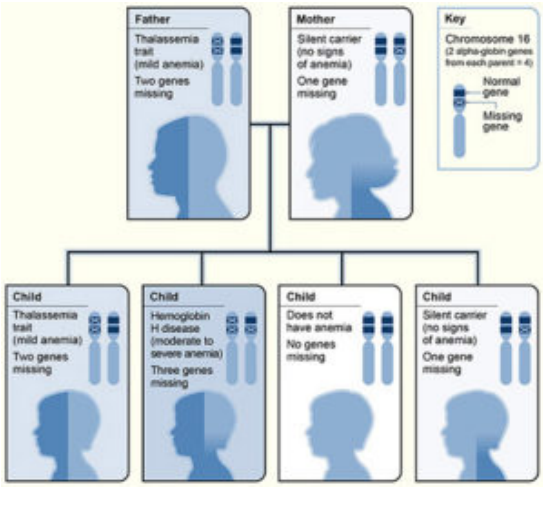


Image: "Thalassemia alpha" The picture shows one example of how alpha thalassemia is inherited. The alpha globin genes are located on chromosome 16. A child inherits four alpha globin genes (two from each parent). In this example, the father is missing two alpha globin genes and the mother is missing one alpha globin gene. Each child has a 25 percent chance of inheriting two missing genes and two normal genes (thalassemia trait), three missing genes and one normal gene (hemoglobin H disease), four normal genes (no anemia), or one missing gene and three normal genes (silent carrier). By National Heart Lung and Blood Institute (NIH). License: Public Domain

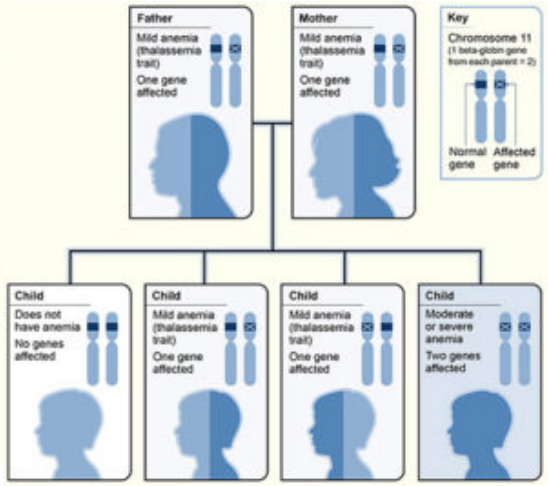


Image: "Thalassemia beta" The picture shows one example of how beta thalassemia is inherited. The beta globin gene is located on chromosome 11. A child inherits two beta globin genes (one from each parent). In this example, each parent has one altered beta globin gene. Each child has a 25 percent chance of inheriting two normal genes (no anemia), a 50 percent chance of inheriting one altered gene and one normal gene (beta thalassemia trait), or a 25 percent chance of inheriting two altered genes (beta thalassemia major). By National Heart Lung and Blood Institute (NIH). License: Public Domain

Pathophysiology

- Defective hemoglobin formation leads to hemoglobin aggregation that damages the RBC membrane

- Damaged RBCs undergo hemolysis that leads to:
    - Anemia
    - Gallstones (pigmented)
- Ineffective erythropoiesis (due to lack of normal hemoglobin components) leads to
    - Anemia → high output heart failure
    - Bone marrow expansion
    - Extramedullary hematopoiesis → hepato and/or splenomegaly
- Iron overload (from multiple need transfusions to account for damaged native RBCs)
    - Compensatory increase in GI uptake of iron
    - Endocrinopathies

Video Gallery

Alpha Thalassemia: Pathogenesis by Carlo Raj, MD
Beta Thalassemia: Morphology and Hemoglobin Electrophoresis by Carlo Raj, MD

Clinical manifestations

Cooley Anemia and HbH Disease

- Anemia
    - Shortness of breath
    - Fatigue
    - Weakness
- Hemolysis
    - Gallstones
    - Splenomegaly
    - Hepatomegaly (Cirrhosis, Spider nevi)
- Bone Marrow Expansion
    - Frontal Bossing
    - Chipmunk Facies
    - Bone pain
    - Fragility fractures
- Malnutrition
- Stunted growth (hypogonadal)

Complications

- Cardiac failure (restrictive or high output)
- Iron overload (secondary hemochromatosis)
    - Arthralgia
    - Bronze skin
    - Cirrhosis
    - Cardiomyopathy
    - DM
    - Hypogonadism
- Transfusion
    - Iron overload
    - Infections
- Thromboembolism

Death: despite management

- In the patient's twenties or thirties
- Iron overload/heart failure

Presentation based on variant	
Disease	**Presentation**
α-thalassemia minima	• Asymptomatic
α-thalassemia minor	• Incidental finding • Mild hypochromic microcytic anemia • Offspring with HbH
HbH disease	• Severe anemia (from birth) • Transfusion dependent
Hb Barts	• In utero • High output cardiac failure: anasarca • Hepatosplenomegaly • Death (in utero) or early infancy
β- thalassemia minor	• Incidental finding • Hypochromic microcytic anemia • Palpable spleen (rare)
β- thalassemia intermedia	• Microcytic anemia • Hepatosplenomegaly • Occasional transfusion
β- thalassemia major (Cooley anemia)	• Severe anemia (~ 6 months of age) • Transfusion dependent

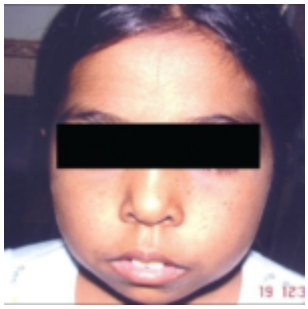


Image: "Frontal bossing and prominent maxilla (thalassemic facies) in a child suffering from thalassemia major." by Taneja R, Malik P, Sharma M, Agarwal MC License: CC BY 2.0

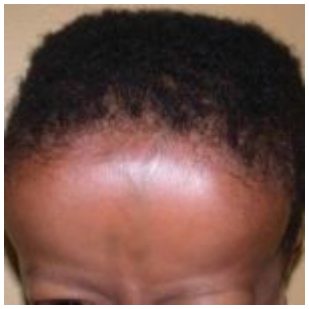


Image: "Frontal bossing (abnormally enlarged forehead) in a child." by US Federal Government. License: Public Domain

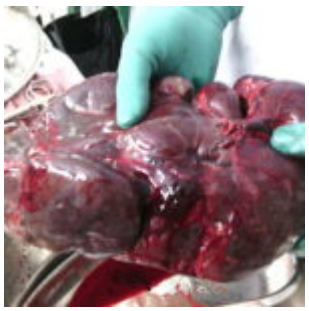


Image: "Surgically removed spleen of a Thalassemic child. it is about 15 times larger than normal." By Almazi. License: CC BY-SA 4.0

Video Gallery

Beta Thalassemia: Clinical Pathology by Carlo Raj, MD

Diagnostics

- Take a full medical history and family history (screen in high-risk areas).
- Order CBC with erythrocyte indices and peripheral blood smear.
- On CBC
    - Hb: usually < 11 g/dL or < 6 g/dL in Cooley anemia
    - MCV: microcytic (< 70 fL) in thalassemias
    - MCH: low in thalassemias
    - RDW: not very useful in thalassemias (can be normal or elevated)
- On peripheral blood smear
    - Target cells (most common)
    - Howell-Jolly body
    - Anisocytosis
    - Inclusion bodies: seen only in HbH disease (4β aggregation)
    - Heinz bodies
    - Basophilic stippling
- **Then, order iron studies (in any anemia) → normal (in thalassemias)**
- If iron studies normal, order a Hb electrophoresis
    - Most **accurate** test
    - In α-thalassemia
        - Minima: normal %
        - Minor (trait): normal % but CBC shows anemia
        - HbH – β-tetrad (i.e. Hb electrophoresis will show only a β band)
        - Hb Barts – γ-tetrad (i.e. Hb electrophoresis will show only a γ band)
    - In β- thalassemia
        - Minor:
            - ↓ HbA (93%)
            - ↑ $HbA_{2>/sub>\ (5\%)}$
            - ↑ HbF (2%)
        - Major:
            - No HbA
            - ↑ HbF(90%)
            - ↑ $HbA_{2>/sub>\ (10\%)}$
- If suspect hemolysis, order LDH – nonspecific elevation, possible hemolysis
    - If LDH elevated and suspect hemolysis, order reticulocyte count (elevated in hemoglobin H disease)
- Other ancillary studies:
    - X-ray will show osteopenia and skull with “hair on end” appearance.
    - Echocardiogram will possibly show a reduction in LVEF.

Mnemonic

To recall the features seen on a Peripheral Blood Smear of a Thalassemia patient, remember **THAL:**

- **T**arget cells (most common)
- **Howell-Jolly body**
- **A**nisocytosis
- **L**ow MCH, MCV, and Hb

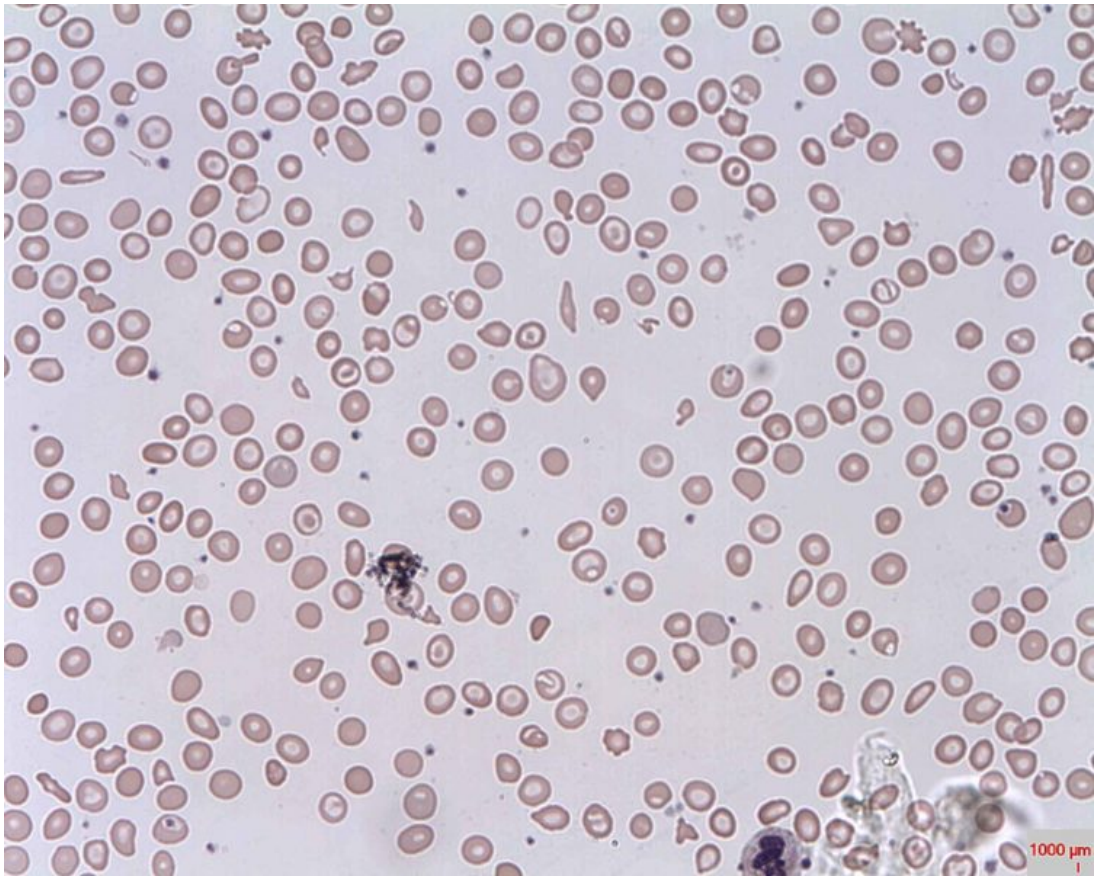


Image: “Target cells” Target cells (Codocytes, Leptocytes, or Mexican hat cells). They are red cells with a central area of intense staining surrounded by a ring of less intensely stained periphery and then a further ring of dense staining at the edge of the cell. Target cells are commonly seen in blood films of patients with liver disease, thalassemia or sickle-cell disease, iron-deficiency anemia, and in splenectomized patients. By Prof. Osaro Erhabor. License: Public Domain

Video Gallery

Alpha Thalassemia: Clinical Pathology by Carlo Raj, MD
Alpha Thalassemia: Hemoglobin Electrophoresis by Carlo Raj, MD

Treatment

This section shows treatments for Cooley anemia and HbH disease.

- Transfusions:
    - Regular blood transfusions (Target Hb level >10 g/dL)
    - Folate if not transfused
- Splenectomy and cholecystectomy:
    - Splenectomies: reduce transfusion requirements
    - Post-splenectomy vaccinations
        - Pneumococcal polyvalent
        - Haemophilus influenzae type b
        - Pneumococcal conjugate
    - Cholecystectomy: prevents recurrent gallstones
- Iron chelation:
    - Deferoxamine (IV)
    - Deferiprone/Deferasirox (PO)
- Endocrine therapy:

        - Administer deficient hormones
        - Bisphosphonates: to prevent osteopenia and osteoporosis
        - Fertility agents
    - Definitive:
        - Allogeneic stem cell transplantation
    - Genetic counseling

Differential Diagnoses

Differentials include other types of hypochromic microcytic anemia and hemolytic anemia.

- **Iron Deficiency Anemia: The most common cause of hypochromic microcytic anemia is due to a deficiency in iron and its reservoir in the body. Very important to differentiate from thalassemia as iron supplementation can worsen thalassemia due to further iron overload.**
- **Anemia of Chronic Disease:** second most common cause of microcytic hypochromic anemia. An imbalance in iron homeostasis secondary to infections, auto-immune disorder, or malignancy. Management of which relies on treating the underlying cause.
- **Sideroblastic Anemia:** It is microcytic anemia in which the bone marrow produces sideroblasts (ring-shaped blood cells) due to the inability of the body to place iron properly into hemoglobin. It presents with abnormal iron studies.
- **Sickle Cell Disease:** hereditary hemoglobinopathy resulting in hypoxia and anemia. The difference is that it is normocytic and sickle-shaped cells are noted on peripheral smear.
- **Hemolytic Anemia:** autoimmune, drug-induced, or Rh-incompatibility present as hemolysis. The difference is that there are auto-immune and the pathologic mechanism is immune-mediated destruction. They also present as normocytic anemia.

Notes