Understanding Thalassemia: Causes, Types, Symptoms, and Treatment

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Learning Objectives

1. **Understand Thalassemia:** Define Thalassemia and its significance in the context of blood disorders.

2. **Comprehend Hemoglobin:** Explain the role of hemoglobin in the blood and how its structure differs in Thalassemia.

3. **Identify Thalassemia Types:** Distinguish between Alpha and Beta Thalassemia, including subtypes and variations.

4. **Explore Genetic Basis:** Describe the genetic inheritance pattern of Thalassemia and identify the genes responsible.

5. **Recognize Symptoms:** Identify common symptoms associated with Thalassemia, as well as the severity levels and potential complications.

Learning Objectives

6. Diagnosis and Screening: Understand the diagnostic methods used to detect Thalassemia, including blood tests and genetic screening.

7. Treatment Options: Explore the various treatment modalities available for managing Thalassemia, such as blood transfusions, chelation therapy, and bone marrow transplants.

What is Thalassemia?

- **Thalassemia** is an inherited blood disorder characterized by the production of an abnormal or insufficient quantity of hemoglobin
- This condition leads to the destruction of a significant number of red blood cells, resulting in the development of anemia.

Genetic Background

Thalassemia has a global incidence of approximately 4.4 cases per 10,000 live births.

Both males and females can inherit the relevant gene mutations, as it follows an autosomal pattern of inheritance.

May involve mutations in Alpha or Beta Globin genes leading to:

- **(α-thalassemia)**
- **(β-thalassemia)**

(Smith, 2022)

Genetic Background

Alpha-thalassemia is particularly common among certain populations of Southeast Asian descent. There are a high number of carriers in Sub-Saharan Africa and Western Pacific regions.

Beta-thalassemia is the most common form of thalassemia among populations of Mediterranean, African, and South Asian ancestry.

Genetic Incidence (Alpha-thalassemia)

America:

- 0-5% of the population has a thalassemia trait
- Up to 40% of this population potentially being genetic carriers.

Eastern Mediterranean:

- 0-2% of the population has a thalassemia trait,
- Up to 60% of this population potentially being genetic carriers.

Europe:

- 1-2% of the population has a thalassemia trait,
- up to 12% of this population being genetic carriers.

Southeast Asia:

- 1-30% of the population has a thalassemia trait
- Up to 40% of this population potentially being genetic carriers

Sub-Saharan Africa:

- 0% of the population has a thalassemia trait and up to
- 50% of this population potentially being genetic carriers.

Western Pacific:

- 0% of the population has a thalassemia trait,
- Up to 60% of this population potentially being genetic carriers

(Center for Disease Control, 2023)

Genetic Incidence (Beta-thalassemia)

Americas:

- 0-3% of the population is affected by a gene mutation

Eastern Mediterranean:

- 2-18% of the population is affected by a gene mutation

Europe:

- 0-19% of the population is affected by a gene mutation

Southeast Asia:

- 0-11% of the population is affected by a gene mutation

Sub-Saharan Africa:

- 0-12% of the population is affected by a gene mutation

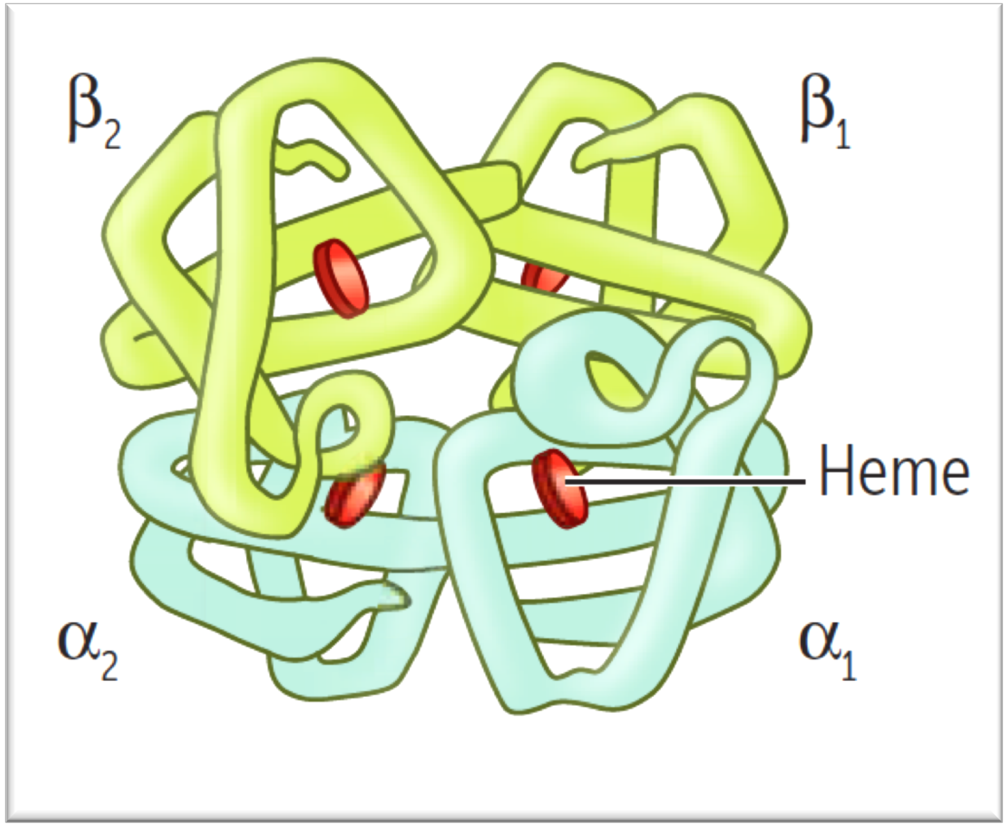
Western Pacific:

- 0-13% of the population is affected by a gene mutation

Center for Disease Control, 2023

Hemoglobin Structure

- Hgb A (predominant)
  - subunits: α_2, $\boldsymbol{\beta_2}$
  - 90-95% of adult hemoglobin
- Hgb A2
  - subunits: α_2,$\boldsymbol{\delta_2}$ (delta)
  - present in trace amounts in adults.
- Hgb F
  - subunits: α_2,$\mathbf{y_2}$ (gamma)
  - declines in the first year of life



(Leonard, 2007)

Alpha vs Beta Thalassemia

Alpha thalassemia:

- Typically a large segment deletion where unequal crossover has deleted one or more alpha globin genes from chromosome 16 during prophase 1
- Note: 4 total genes on 2 chromosomes for alpha chain

Beta thalassemia:

- Synthesis of β-globin chain is decreased or absent, typically as a result of point mutations on chromosome 11 that affect the production of functional mRNA
- Most often, mutations occur in the promoter regions preceding the beta globin genes
- Splice site variants are also believed to contribute to the disease

(Leonard, 2007)

Alpha Thalassemia

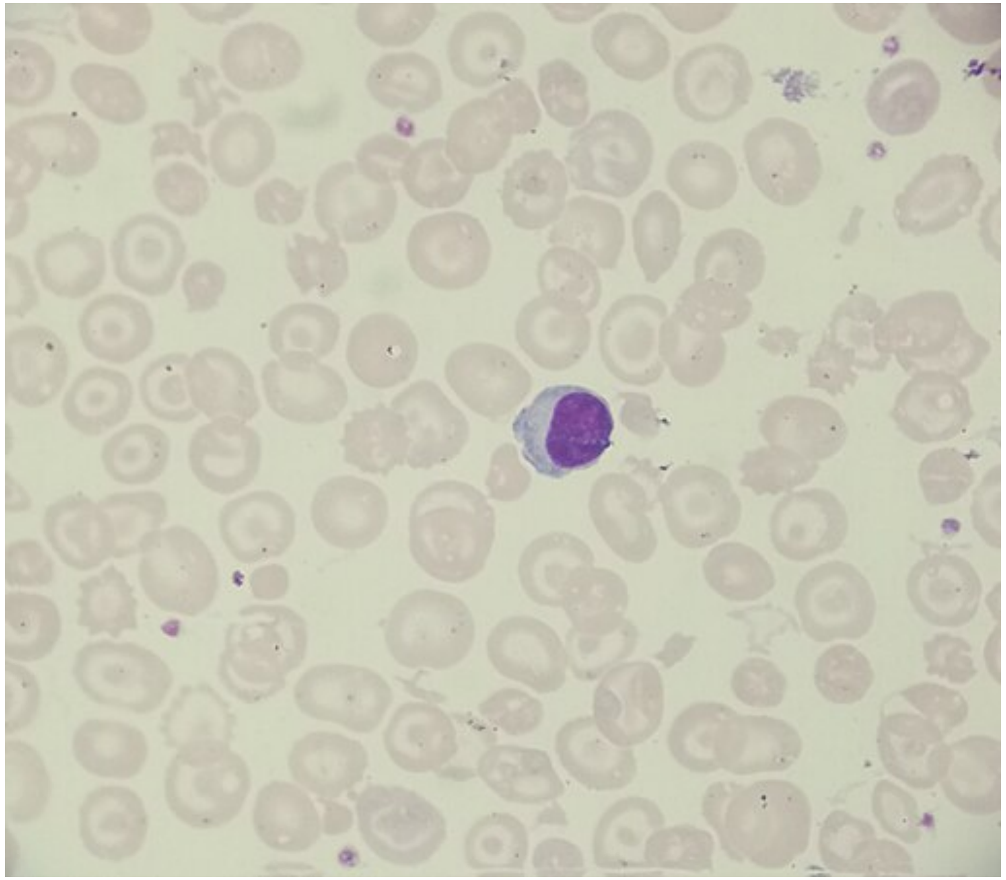
- 4 total copies of genes for alpha globin on chromosome 16
- Symptoms range from asymptomatic (carrier) to Hydrops Fetalis.
- 2 main pathologies:
  - Hemoglobin H
  - Hemoglobin Bart Disease

Number of Globin Genes	Genotype	Description	Clinical Features
4	αα/αα	Normal	Normal
3	α-/αα	Heterozygous alpha thalassemia	Asymptomatic
2	α-/α-	Homogyzgous alpha thalassemia	Mild Microcytic anemia
	αα/--	Heterozygous alpha thalassemia	Mild Microcytic anemia
1	α-/--	Hemoglobin H Disease	Hemolytic anemia, splenomegaly, bone changes, iron overload
0	--/--	Hemoglobin Bart Disease	Hydrops Fetalis

(Leonard, 2007)

Hemoglobin H & Hemoglobin Bart Disease

- 2 main pathologies:
  - Hemoglobin H
    - Beta globin chains bind together
    - 3 genes deleted leading to severe anemia
  - Hemoglobin Bart Disease
    - 4 genes deleted causing globin chains to form tetramers → hydrops



(Leonard, 2007)

Beta Thalassemia

Defective Beta globin genes located on chromosome 11 leading to:

- β-thalassemia trait (β-thalassemia minor) if they have only one defective β-globin gene,

or

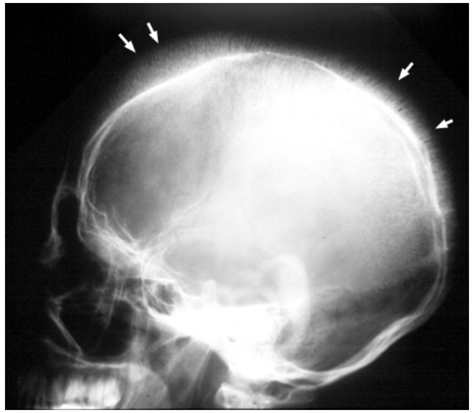
- β-thalassemia major (Cooley anemia) if both genes are defective.

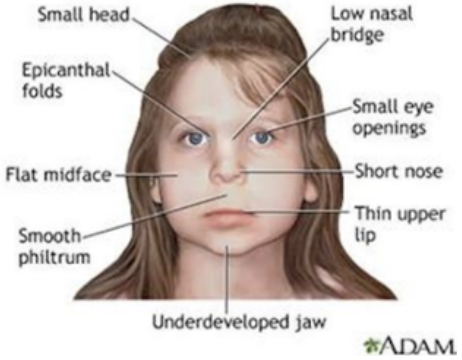
Common Genotypes	Name	Phenotype
β/β	Normal	None
β/β^0 β/β^+	Beta thalassemia trait	Thalassemia minor: asymptomatic, mild, microcytic hypochromic anemia
β^+/β^+ β^+/β^0 β^E/β^+ β^E/β^0	Beta thalassemia intermedia	Variable severity Mild to moderate anemia Possible extramedullary hematopoiesis Iron overload
β^0/β^0	Beta thalassemia major (Cooley's Anemia)	Severe anemia Transfusion dependence Extramedullary hematopoiesis Iron Overload

(Leonard, 2007)

Cooley’s Anemia

- Characterized by:
  - Severe anemia
  - Hepatosplenomegaly due to chronic hemolysis
  - Extramedullary hematopoiesis
  - “Crew cut/ Hair on end appearance” on X-ray
  - “Chipmunk facies” secondary to extramedullary hematopoiesis
- Symptoms begin after several months of life
- Therapy such as blood transfusions, iron chelation
- Often associated with **cardiac complications**.





(Leonard, 2007)

Diagnosis of Thalassemia

- Your health care provider will do a physical exam to look for an enlarged spleen.
- A blood sample will be sent to a laboratory to be tested. Red blood cells will appear small and abnormally shaped when looked at under a microscope.
- A complete blood count (CBC) reveals anemia.
- A test called hemoglobin electrophoresis shows the presence of an abnormal form of hemoglobin.
- A test called mutational analysis can help detect alpha thalassemia.

(U.S. National Library of Medicine, 2022)

Treatment Options

- Blood transfusions
- Chelation therapy
- Bone marrow transplant
- Gene therapy (if applicable)

Treatment for thalassemia major often involves regular blood transfusions and folate supplements.

People who receive a lot of blood transfusions need chelation therapy to remove excess iron from the body.

A bone marrow transplant may help treat the disease in some people, especially children.

U.S. National Library of Medicine, 2022

CME Question

- A 6-year-old child presents to the pediatric clinic with complaints of fatigue, pale skin, and delayed growth. The physical examination reveals hepatosplenomegaly, jaundice, and skeletal deformities. Lab results show severe anemia, microcytosis, and a hemoglobin electrophoresis indicating beta-thalassemia major. Given this clinical scenario, what are the key diagnostic features, treatment options, and potential complications that should be discussed with the child's parents?
- A) Genetic counseling and prenatal testing for future pregnancies
- B) Blood transfusion and iron chelation therapy
- C) Physical therapy for skeletal deformities
- D) Lifestyle modifications to improve growth and energy levels

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CME Question

- In the case of beta-thalassemia major (Cooley's anemia), regular blood transfusions are often necessary to manage severe anemia. Iron chelation therapy is essential to address iron overload resulting from repeated transfusions.

- The other options, such as genetic counseling (A), physical therapy for skeletal deformities (C), and lifestyle modifications (D), may also be important aspects of care, but the immediate priority in managing severe beta-thalassemia major is blood transfusion and iron chelation therapy.

References

1) Centers for Disease Control and Prevention. (2023, April 24). *What is thalassemia?*. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/thalassemia/facts.html

2) Smith, Yolanda. (2022, August 30). Thalassemia Prevalence. News-Medical. Retrieved on September 03, 2023 from https://www.news-medical.net/health/Thalassemia-Prevalence.aspx.

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4) U.S. National Library of Medicine. (2022, Jan 25.). *Thalassemia: Medlineplus medical encyclopedia*. MedlinePlus. https://medlineplus.gov/ency/article/000587.htm