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Thalassemia: An Overview of Genetics, Pathophysiology and Management

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Abstract:

Thalassemia is a group of inherited haemoglobin disorders resulting in reduced or absent production of one or more globin chains, leading to chronic anemia and multisystem complications. It significantly impacts quality of life and places a burden on healthcare systems, especially in regions where it is endemic. The clinical spectrum ranges from asymptomatic carrier states to severe transfusion-dependent disease. Advances in blood transfusion practices, iron chelation therapy, stem cell transplantation, and emerging gene-based treatments have substantially improved outcomes. This review discusses the introduction, classification, pathophysiology, management, and future directions of thalassemia. Thalassemia is a genetically inherited blood disorder characterized by reduced or absent production of globin chains, leading to an imbalance in haemoglobin synthesis and chronic anemia. The disease is marked by ineffective erythropoiesis, increased red blood cell destruction, bone marrow expansion, and iron overload, which collectively contribute to progressive organ damage. The severity of thalassemia varies widely depending on the type and number of affected globin genes. Regular blood transfusions remain the cornerstone of treatment for severe forms; however, transfusion-related iron overload necessitates long-term chelation therapy. Curative approaches such as hematopoietic stem cell transplantation and novel gene-based therapies have emerged as promising treatment modalities. This review discusses the molecular and cellular mechanisms underlying thalassemia, along with current and emerging treatment strategies aimed at improving long-term outcomes and quality of life.

Keywords: Thalassemia, Anemia, Jaundince, Skeletal Abnormalities, Erythropoiesis

1. INTRODUCTION

Thalassemia refers to a group of genetic disorders characterized by defective synthesis of globin chains, the protein components of haemoglobin, leading to varying degrees of anemia and organ damage. Haemoglobin is essential for transporting oxygen from the lungs to tissues; any disruption in its formation results in impaired oxygen delivery and chronic hypoxia, which contribute to the clinical manifestations of thalassemia [1].

The most common forms involve the alpha and beta globin chains. Thalassemia is inherited in an autosomal recessive pattern, meaning an affected individual inherits defective genes from both parents. Individuals with one defective gene are carriers and usually asymptomatic, while those with mutations in both genes suffer from more severe disease [2].

Thalassemia has a high global prevalence, particularly in regions historically affected by malaria because carrier status confers a survival advantage against the infection. The carrier frequency can be as high as 10–40% in parts of the Mediterranean, Middle East, South Asia, and Southeast Asia [3]. Migration has led to the global spread of thalassemia, making it a major public health issue in many countries.

Clinically, untreated severe thalassemia results in growth retardation, bone deformities, poor quality of life, and early mortality. With advances in medical care, however, many patients now survive into adulthood. Comprehensive management includes regular blood transfusions, iron chelation therapy, and in some cases, curative treatments such as hematopoietic stem cell transplantation [4].

2. CLASSIFICATION OF THALASSEMIA

Thalassemia is classified based on the affected globin chain. The two major forms are alpha thalassemia and beta thalassemia, with additional subtypes and rare variants that influence disease severity and clinical management [5].

2.1 Alpha Thalassemia

Alpha thalassemia arises from decreased or absent synthesis of alpha globin chains due to deletions or mutations in the alpha globin genes located on chromosome 16. Humans typically have four alpha globin genes, and the number of affected genes determines disease severity [6].

When one alpha globin gene is deleted, the individual is a silent carrier and usually asymptomatic. Deletion of two genes leads to alpha thalassemia trait, which may cause mild anemia often mistaken for iron deficiency anemia unless properly investigated [7].

Deletion of three genes causes Hemoglobin H disease, characterized by moderate to severe haemolytic anemia, splenomegaly, and jaundice. The absence of all four alpha globin genes results in haemoglobin Bart's hydrops fetalis, a usually fatal condition in utero due to severe oxygen deprivation [8].

2.2 Beta Thalassemia:

Beta thalassemia results from mutations in the beta globin gene on chromosome 11, leading to reduced (β^+) or absent (β^0) beta globin chain production. The severity depends on the specific mutation and whether one or both alleles are affected [9].

Beta thalassemia minor (trait) occurs in heterozygous individuals who generally exhibit mild microcytic anemia and are often asymptomatic. Beta thalassemia intermedia is characterized by moderate anemia and variable transfusion requirements, reflecting partial suppression of beta globin synthesis [10].

The most severe form, beta thalassemia major (Cooley's anemia), presents in infancy with profound anemia, jaundice, skeletal abnormalities, and failure to thrive. Without regular transfusions, this form is life-threatening, underscoring the importance of early diagnosis and comprehensive care [11].

2.3 Hemoglobin E–Thalassemia:

Hemoglobin E (HbE) thalassemia is a common variant in Southeast Asia, resulting from a combination of hemoglobin E (a structural variant of beta globin) and beta thalassemia mutations. Clinical severity varies widely, from mild anemia to a severe, transfusion dependent state similar to beta thalassemia major, influenced by genetic modifiers and environmental factors [12].

2.4 Delta-Beta and Other Rare Variants:

Delta-beta thalassemia involves deletions of both delta and beta globin genes, leading to increased fetal hemoglobin (HbF) that can partially ameliorate anemia. Other rare combinations, such as hereditary persistence of fetal hemoglobin (HPFH), result in high HbF levels and a relatively mild clinical course. Understanding these variants is essential for accurate diagnosis, prognosis, and genetic counseling [13].

3. PATHOPHYSIOLOGY

The underlying pathophysiology of thalassemia revolves around an imbalance in globin chain synthesis. Normal erythropoiesis requires balanced production of alpha and beta globin chains; disruption leads to accumulation of unpaired globin chains, causing toxic effects within erythroid cells [14].

3.1 Ineffective Erythropoiesis:

Excess unpaired globin chains precipitate within erythroid precursors in the bone marrow, causing oxidative damage and apoptosis. This phenomenon, termed ineffective erythropoiesis, is a hallmark of thalassemia and results in markedly increased but ineffective bone marrow activity [15].

The resulting severe anemia stimulates erythropoietin production, leading to expansion of hematopoietic tissue. This compensatory response causes bone marrow expansion, cortical thinning, and characteristic skeletal deformities involving the face, skull, and long bones [16].

3.2 Hemolysis:

In addition to ineffective erythropoiesis, circulating red blood cells that manage to mature are structurally defective and have reduced survival. These cells are prone to premature destruction by the spleen, contributing to chronic hemolysis and further exacerbating anemia [17].

3.3 Iron Overload:

Iron overload is a central pathological feature of thalassemia, arising from both increased intestinal iron absorption driven by ineffective erythropoiesis and repeated blood transfusions. The body lacks an active mechanism to excrete excess iron, leading to its deposition in the liver, heart, and endocrine organs. Free iron catalyzes the formation of reactive oxygen species, causing cellular injury, fibrosis, and organ dysfunction [18].

Cardiac iron deposition is the leading cause of mortality in transfusion-dependent individuals, often resulting in cardiomyopathy and arrhythmias if not effectively managed. Hepatic iron overload predisposes to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma. Endocrine gland involvement leads to diabetes mellitus, growth hormone deficiency, hypothyroidism, and hypogonadism [19].

4. TREATMENT

Managing thalassemia requires an individualized, lifelong approach involving both supportive and curative strategies, tailored to disease severity and patient needs [20].

4.1 Blood Transfusion Therapy:

Regular red blood cell transfusions are the mainstay of treatment for patients with thalassemia major and some cases of thalassemia intermedia. Transfusions aim to maintain hemoglobin levels adequately high to suppress bone marrow overactivity and reduce the symptoms of anemia. However, chronic transfusion therapy carries the risk of iron overload, necessitating effective iron chelation [21].

4.2 Iron Chelation Therapy:

Iron chelation is essential to prevent iron-induced organ damage. Three primary chelators are used: deferoxamine (parenteral), deferiprone (oral), and deferasirox (oral). Deferoxamine, while effective, requires prolonged subcutaneous infusions, leading to compliance challenges. Oral agents have

improved convenience and adherence. Combination chelation may be used in patients with severe iron burden, especially cardiac iron overload [22].

4.3 Splenectomy:

Splenectomy may be indicated in patients with hypersplenism who require excessive transfusions or develop significant cytopenias. While this procedure can reduce transfusion requirements, it is associated with long-term risks, including thrombosis and severe infections, particularly by encapsulated bacteria. Lifelong vaccinations and antibiotic prophylaxis are recommended post-splenectomy [23].

4.4 Curative Therapies:

4.4.1 Hematopoietic Stem Cell Transplantation:

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only established curative treatment for thalassemia. It is most successful when performed during childhood with a matched sibling donor, resulting in normal hemoglobin production and cessation of transfusion dependence. Risks include graft-versus-host disease, infections, and transplant-related mortality, but outcomes have improved with advances in conditioning regimens and supportive care [24].

4.4.2 Gene Therapy:

Gene therapy represents a rapidly evolving curative approach. Techniques include adding functional globin genes using lentiviral vectors and gene editing (e.g., CRISPR-Cas9) to reactivate fetal hemoglobin production. Early clinical trials have demonstrated transfusion independence in several patients, offering promising long-term prospects [25].

4.5 Supportive Care:

Supportive care, including folic acid supplementation, management of bone disease, and monitoring for complications (cardiac, endocrine, hepatic), is integral to comprehensive thalassemia care. Multidisciplinary teams improve outcomes by addressing both medical and psychosocial needs [26].

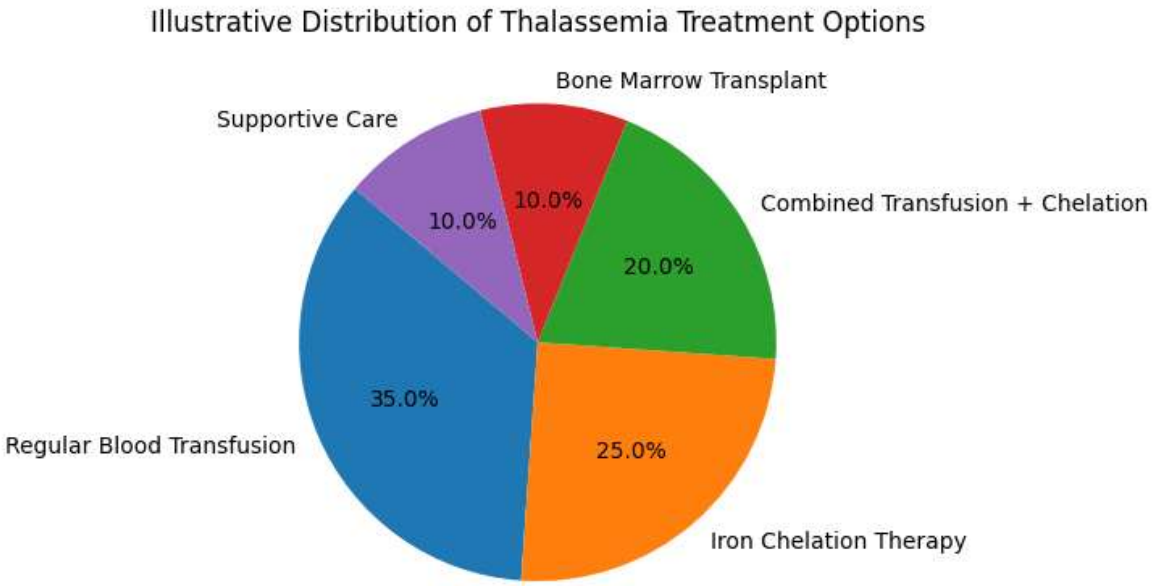

Figure 1: Treatment Modalities for Thalassemia Patients

Bone Marrow Transplant: 10%

Combined Transfusion + Chelation: 20%

Iron Chelation Therapy: 25%

Regular Blood Transfusion: 35%

Supportive Care: 10%

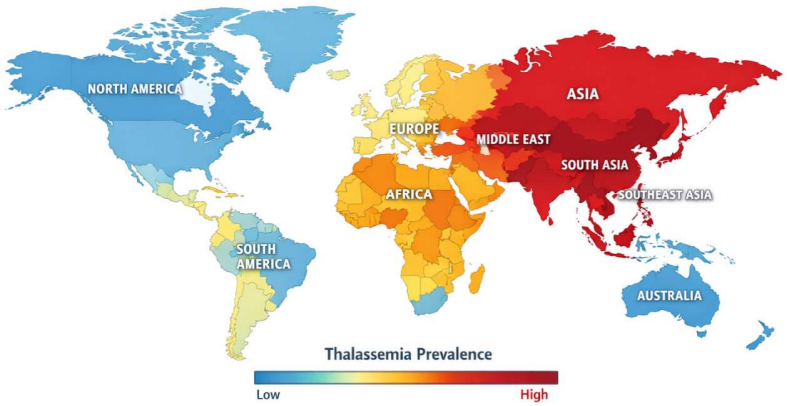

Figure 2: Map Of Global Thalassemia Prevalence

5. Relationship Between Genes And Disease Severity

Types	Genes Effected	Symptoms	Treatment
Alpha(1 gene)	1/4	No symptoms	None
Alpha(2 gene)	2/4	Mild anemia	Occasionally monitaring
Alpha(3gene)	3/4	Moderate	Transfusion, chelation
Alpha(4 gene)	4/4	Fatal	Intensive care
Alpha(1 gene)	1/2	Mild anemia	None
Alpha(2 gene)	2/2	Sever anemia	Regular transfusion ortransplants

6. Discussion

Thalassemia continues to exert a significant global health burden, particularly in low- and middle-income countries where resources for comprehensive care may be limited. Early diagnosis through newborn screening and carrier detection programs can facilitate timely intervention and reduce disease burden [27].

Population screening and genetic counseling have proven effective in reducing affected births in countries with high disease prevalence. Programs that integrate public education, premarital screening, and prenatal diagnosis enable informed reproductive choices, leading to declines in severe thalassemia births over time [28].

The psychosocial impact of thalassemia should not be underestimated. Chronic disease management affects not only physical health but also emotional well-being, education, employment, and family dynamics. Structured psychosocial support and patient-centered care models have been shown to improve quality of life and adherence to treatment [29].

Emerging therapies, particularly gene editing and pharmacologic agents targeting ineffective erythropoiesis (such as luspatercept), hold promise for reducing transfusion requirements and improving long-term outcomes. Continued research into the molecular mechanisms of thalassemia and innovative treatment strategies is essential to further improve patient care [30].

7. Conclusion

Thalassemia is a complex inherited disorder that significantly affects patients' lives and healthcare systems worldwide. Advances in medical care have transformed the prognosis for many, but challenges remain in achieving equitable access to comprehensive treatment and curative therapies.

Continued efforts in early detection, multidisciplinary care, genetic counseling, and innovative therapeutic development are vital for further progress.

Thalassemia represents a lifelong condition that requires sustained medical care and patient adherence to complex treatment regimens. While supportive therapies such as blood transfusions and iron chelation remain the cornerstone of management, emerging curative strategies have transformed the therapeutic landscape. Hematopoietic stem cell transplantation and innovative gene therapy approaches hold the potential to eliminate disease burden in selected patients. Strengthening healthcare infrastructure, expanding screening programs, and integrating novel therapies into routine practice are critical steps toward reducing disease-related morbidity and mortality. Continued advancements in personalized medicine are expected to further improve outcomes for individuals living with thalassemia.

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