Thalassemias

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KEYWORDS

• Thalassemia • Iron overload • Hemoglobinopathies • Anemia

KEY POINTS

- The thalassemia syndromes are a heterogeneous group of disorders characterized by variable degrees of hemolysis, chronic anemia, and ineffective erythropoiesis.
- Because more patients are living longer, disease- and treatment-related complications are becoming more common.
- Optimal and safe transfusion support, iron chelation, noninvasive iron assessments, and stem cell therapies provide new tools for effective management of thalassemia.

INTRODUCTION/HISTORY

The thalassemia syndromes are a group of inherited hemoglobinopathies that result from significantly reduced or absent synthesis of normal hemoglobin. The type of thalassemia is based on the defective globin gene involved; patients with affected β-globin genes have β-thalassemia, and those with affected α-globin genes have α-thalassemia. Patients with thalassemia have widely variable clinical presentations, ranging from nearly asymptomatic to severe anemia requiring lifelong blood transfusions with complications in multiple organ systems. The mainstay of therapy for thalassemia remains red blood cell transfusion, which then necessitates iron chelation. This article focuses on the diagnosis and clinical manifestations of thalassemia.

EPIDEMIOLOGY

Although thalassemia is rare in the United States, an estimated 5% of the world's populations carry at least one variant globin allele.[1] In general, these conditions are inherited in an autosomal recessive pattern. Numerous studies have confirmed that red blood cells in thalassemia carriers are less susceptible to invasion by *Plasmodium falciparum*, thus conferring a survival advantage in malaria-endemic regions.[2] The prevalence of thalassemia is highest in geographic regions that historically were most affected by malaria, including the Mediterranean, sub-Saharan Africa, the Middle

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East, the Asian-Indian subcontinent, and Southeast Asia. Resources available in many regions have substantially improved patient survival over time.[3] In 1973, fewer than 2% of patients with thalassemia were older than 25 years; today that cohort represents 36% of patients with thalassemia in the United States. Immigration has also contributed to the ethnic diversity of the thalassemia population in the United States.[4]

α-THALASSEMIA

α-Thalassemia is caused by absent or decreased production of α-globin chains. The α gene locus contains paired alleles (αα/αα) on chromosome 16. Clinical severity varies based on the number of alleles affected and also on the type of genetic mutation.[5] Deletional defects involving the α-globin gene locus can be from nonhomologous recombination or other mechanisms that either completely or at least partially delete both α-globin chains. Nondeletional mutations result in reduced production of α-globin and, in some cases, varying amounts of structurally aberrant α-globins that are associated with a more severe clinical phenotype.

Persons with one mutated allele are silent carriers (αα/α-). Patients with α-thalassemia trait have 2 deletions (αα/–) on the same chromosome (*cis*) or on opposite (α-/α-) chromosomes (*trans*.). The arrangement of these anomalies have important implications on reproduction. Inheritance of 2 mutant α alleles in *cis* from one parent, combined with a single mutation from a parent who is a silent carrier, may result in a clinically significant condition involving 3 of 4 genes in the offspring. α-Thalassemia involving all 4 α genes typically has a severe clinical phenotype, often causing intrauterine anemia and hydrops fetalis.[6]

Hemoglobin H (HbH) disease is caused by mutations of 3 of the 4 alleles, with compound heterozygosity for α^+ and α^0 mutations. In fetal development, the excess γ chains form homotetramers (γ_4), also called *Hb Bart's*, which are detectable transiently at birth. Later, excess β-globin chains form β_4 homotetramers (HbH), which are unstable and precipitate in developing red cells. The globin chain imbalance contributes to ineffective erythropoiesis and local intracellular oxidative damage in circulating red blood cells and shortened red cell life span. Most patients with HbH disease are not transfusion-dependent but may require transfusion support for infections and other oxidative stresses.[7,8]

The most common nondeletional form of HbH disease is HbH Constant Spring. The Constant Spring α-globin mutation results in the elongation of 3′ mRNA sequences, abnormally elongated α-globin chains, and reduced globin production from the unaffected allele.[8] Intracellular precipitation of oxidized chains of hemoglobin Constant Spring damages red cell membranes, which causes hemolysis and a more severe anemia. Unlike most other forms of HbH disease, patients with HbH Constant Spring are often transfusion-dependent.

β-THALASSEMIA

The β-globin locus on chromosome 11 includes genes that encode γ-, δ-, and β-globins, which pair with α-globin chains to create fetal hemoglobin (HbF), hemoglobin A_2, and normal adult hemoglobin (HbA), respectively. Hundreds of β-globin gene mutations cause β-thalassemia, involving both coding and intervening (noncoding) DNA sequences. The disease severity, or degree of transfusion dependence, correlates with the degree of α-globin chain excess.[9] Patients usually present with anemia as early as the first 6 months of life when HbF production declines,[10] or they can present in early childhood with symptoms such as abdominal distention, hepatosplenomegaly from extramedullary hematopoiesis, irritability, jaundice, and poor growth.