

PediatricsⁱⁿReview[®]

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Pediatrics in Review 2012;33;434

DOI: 10.1542/pir.33-9-434

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In Brief

Thalassemia

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Author Disclosure

Dr Kelly has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Thalassemia is a group of inherited blood disorders caused by defects in one or more genes responsible for producing the globin chains in hemoglobin. The

clinical syndromes are the result of two problems. First, insufficient synthesis of either α - or β -globin leads to inadequate production of the predominant adult hemoglobin A ($\alpha_2\beta_2$) and results in microcytosis (low mean corpuscular volume) and hypochromia (low mean corpuscular hemoglobin). Second, diminished synthesis of one type of globin leads to a relative excess of the globin with which it would normally pair. Excess unpaired globin chains form unstable tetramers that precipitate in red blood cells, causing impaired erythropoiesis or hemolysis.

α -Thalassemia Syndromes

α -Thalassemia occurs when there is a defect or deletion in one or more of the four genes responsible for α -globin production, leading to insufficient or absent α -globin synthesis.

A defect or deletion of one α -globin gene leads to a condition called silent trait that is completely asymptomatic.

The presence of two defective α -globin genes causes α -thalassemia trait, manifesting as a mild microcytic, hypochromic anemia. Hemoglobin electrophoresis can aid in diagnosis, but only during the neonatal period, when hemoglobin Bart is detected at 3% to 10%. Because hemoglobin F predominates at birth, impaired production of α -globin chains results in excess unpaired γ -globin chains that form tetramers, making hemoglobin Bart. After birth, as the infant's dominant hemoglobin transitions from F to A, γ -globin chain production subsides, and hemoglobin Bart is no longer detected. No treatment is necessary for α -thalassemia trait.

The presence of three defective α -globin genes causes hemoglobin H disease. Hemoglobin Bart is detected (15%–30%) on electrophoresis during

the neonatal period. Later in life, when hemoglobin A should predominate, excess unpaired β -globin chains accumulate and form tetramers, making hemoglobin H. Unstable hemoglobin H precipitates in circulating red blood cells, leading to hemolysis. Patients have microcytic, hypochromic anemia and hepatosplenomegaly, and also may have bony abnormalities resulting from marrow expansion, as well as cholelithiasis and icterus. Transfusion usually is not required, but occasionally patients require splenectomy.

Hydrops fetalis occurs when all four α -globin genes are defective or absent. In the affected fetus, no α -globin chains are synthesized, and hemoglobin Bart is the predominant hemoglobin. Oxygen delivery to tissues is severely impaired and the affected fetus has profound anemia, hepatosplenomegaly, and anasarca, and usually is stillborn or dies shortly after birth. Lifelong transfusion therapy is required for those infants who survive.

β -Thalassemia Syndromes

β -Thalassemia occurs if one or both of the two genes responsible for β -globin production is mutated or deleted, leading to insufficient or no β -globin synthesis.

β -Thalassemia minor (trait) results from the inheritance of one defective gene for β -globin synthesis. Patients usually have significant microcytosis and hypochromia, but only mild anemia. In β -thalassemia trait, hemoglobin electrophoresis results in the neonatal period are normal, but by ~ 1 year of age, hemoglobin A₂ (usually greater than 3.5%) and/or F are elevated because of increased synthesis of δ - and/or γ -globin chains, respectively. No treatment is necessary for β -thalassemia minor.

β -Thalassemia intermedia occurs as a result of a variety of mutations involving the β -globin genes but causes less significant disease than β -thalassemia major. These patients usually have significant microcytic hypochromic anemia but do not require chronic transfusions.

β -Thalassemia major, or Cooley anemia, occurs when two defective β -globin genes are inherited. No β -globin chains are synthesized, so hemoglobin A cannot be produced. Affected infants usually are born healthy, having only hemoglobin F detected on electrophoresis in the neonatal period. Symptoms usually develop in the second six months after birth, when the transition in hemoglobin predominance from F to A should occur. Patients have marked microcytic, hypochromic anemia. Excess α -globin chains precipitate, leading to ineffective erythropoiesis and hemolytic anemia. Patients may exhibit irritability, poor growth, jaundice, hepatosplenomegaly, and high-output congestive heart failure. To compensate for the profound anemia, massive bone marrow expansion occurs, resulting in characteristic facial features of maxillary hyperplasia and frontal bossing. Treatment consists of chronic transfusions and iron chelation or hematopoietic stem cell transplantation.

α -Thalassemia trait, β -thalassemia minor, and iron deficiency are the most

common causes of microcytic anemia and must be differentiated to ensure proper treatment and genetic counseling. Iron deficiency anemia may be diagnosed if a child has low serum ferritin and a normal C-reactive protein (CRP). Because serum ferritin is an acute phase reactant, it can be falsely elevated in inflammatory states. A normal CRP is therefore necessary to ensure the serum ferritin level is truly reflective of the child's iron status. Reticulocyte hemoglobin concentration (CHr) also may be used to diagnose iron deficiency. Standard values for children have been determined, and a low CHr is a strong predictor of iron deficiency.

α -Thalassemia can be diagnosed by identification of Bart hemoglobin on newborn screening. β -Thalassemia is diagnosed when hemoglobin electrophoresis done in early childhood demonstrates elevated levels of A_2 as described previously.

Comments: The term "thalassemia" comes from a derivative of a Greek term that translates as "the sea" in the blood (Mediterranean Sea). Thalassemia is seen most commonly in areas of the world where malaria is prevalent, because heterozygotic individuals experience some protection against malaria, similar to the protection those who have sickle cell trait experience.

Although thalassemia can affect many different ethnic groups, it occurs most commonly in patients from countries around the Mediterranean and regions of Asia and Africa. Gene mapping has determined that the defects for the globin genes are on chromosomes 11 and 16. There are at least 200 different mutations, but 15 mutations cause the vast majority of symptoms in patients. Prenatal diagnosis is possible and can lead to genetic counseling for the most serious variants. Ongoing research is exploring new therapies for severe cases; areas of focus include stimulation of γ -globin expression and replacement of the defective β globin genes.

It is important for health-care professionals to consider α - and β -thalassemia trait in conjunction with iron deficiency when considering the differential of microcytic anemia. A normal red blood cell distribution width and free erythrocyte protoporphyrin usually are present in thalassemia trait, in contrast to prolonged red blood cell distribution width and elevated free erythrocyte protoporphyrin in patients with iron deficiency anemia. Differentiating these entities will result in sparing unnecessary iron therapy for those with thalassemia trait.

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