TABLE 127-4 THE α THALASSEMIAS

Condition	Hemoglobin A, %	Hemoglobin H (β4), %	Hemoglobin Level, g/L (g/dL)	MCV, fL
Normal	97	0	150 (15)	90
Silent thalassemia: –α/αα	98–100	0	150 (15)	90
Thalassemia trait: –α/–α homozygous α-thal-2[a] or ––/αα heterozygous α-thal-1[a]	85–95	Rare red blood cell inclusions	120–130 (12–13)	70–80
Hemoglobin H disease: ––/–α heterozygous α-thal-1/α-thal-2	70–95	5–30	60–100 (6–10)	60–70
Hydrops fetalis: ––/–– homozygous α-thal-1	0	5–10[b]	Fatal in utero or at birth	

[a]When both α alleles on one chromosome are deleted, the locus is called α-thal-1; when only a single α allele on one chromosome is deleted, the locus is called α-thal-2. [b]90–95% of the hemoglobin is hemoglobin Barts (tetramers of γ chains).

α thalassemia-1 trait, with two deleted loci; HbH disease, with three loci deleted; and hydrops fetalis with Hb Barts, with all four loci deleted (Table 127-4). Nondeletion forms of α thalassemia also exist.

α Thalassemia-2 trait is an asymptomatic, silent carrier state. *α Thalassemia-1 trait* resembles β thalassemia minor. Offspring doubly heterozygous for α thalassemia-2 and α thalassemia-1 exhibit a more severe phenotype called *HbH disease*. Heterozygosity for a deletion that removes both genes from the same chromosome (*cis* deletion) is common in Asians and in those from the Mediterranean region, as is homozygosity for α thalassemia-2 (*trans* deletion). Both produce asymptomatic hypochromia and microcytosis.

In *HbH disease*, HbA production is only 25–30% normal. Fetuses accumulate some unpaired γ chains (Hb Barts; γ-chain tetramers). In adults, unpaired β chains accumulate and are soluble enough to form β_4 tetramers called HbH. HbH forms few inclusions in erythroblasts and precipitates in circulating RBC. Patients with HbH disease have thalassemia intermedia characterized by moderately severe hemolytic anemia but milder ineffective erythropoiesis. Survival into midadult life without transfusions is common.

The homozygous state for the α thalassemia-1 *cis* deletion (hydrops fetalis) causes total absence of α-globin synthesis. No physiologically useful hemoglobin is produced beyond the embryonic stage. Excess γ globin forms tetramers called *Hb Barts* (γ_4), which has a very high oxygen affinity. It delivers almost no O_2 to fetal tissues, causing tissue asphyxia, edema (hydrops fetalis), congestive heart failure, and death in utero. α Thalassemia-2 trait is common (15–20%) among people of African descent. The *cis* α thalassemia-1 deletion is almost never seen, however. Thus, α thalassemia-2 and the *trans* form of α thalassemia-1 are very common, but HbH disease and hydrops fetalis are rare.

It has been known for some time that some patients with myelodysplasia or erythroleukemia produce RBC clones containing HbH. This phenomenon is due to mutations in the ATRX pathway that affect the LCR of the α-globin gene cluster.

DIAGNOSIS AND MANAGEMENT OF THALASSEMIAS

The diagnosis of β-thalassemia major is readily made during childhood on the basis of severe anemia accompanied by the characteristic signs of massive ineffective erythropoiesis: hepatosplenomegaly, profound microcytosis, a characteristic blood smear (Fig. 127-5), and elevated levels of HbF, HbA_2, or both. Many patients require chronic hypertransfusion therapy designed to maintain a hematocrit of at least 27–30% so that erythropoiesis is suppressed. Splenectomy is required if the annual transfusion requirement (volume of RBCs per kilogram of body weight per year) increases by >50%. Folic acid supplements may be useful. Vaccination with Pneumovax in anticipation of eventual splenectomy is advised, as is close monitoring for infection, leg ulcers, and biliary tract disease. Many patients develop endocrine deficiencies as a result of iron overload. Early endocrine evaluation is required for glucose intolerance, thyroid dysfunction, and delayed onset of puberty or secondary sexual characteristics.

Patients with β thalassemia intermedia exhibit similar stigmata but can survive without chronic hypertransfusion. Management is particularly challenging because a number of factors can aggravate the anemia, including infection, onset of puberty, and development of splenomegaly and hypersplenism. Some patients may eventually benefit from splenectomy. The expanded erythron can cause absorption of excessive dietary iron and hemosiderosis, even without transfusion. Some patients eventually become transfusion dependent.

β Thalassemia minor (i.e., thalassemia trait) usually presents as profound microcytosis and hypochromia with target cells, but only minimal or mild anemia. The mean corpuscular volume is rarely >75 fL; the hematocrit is rarely <30–33%. Hemoglobin analysis classically reveals an elevated HbA_2 (3.5–7.5%), but some forms are associated with normal HbA_2 and/or elevated HbF. Genetic counseling and patient education are essential. Patients with β thalassemia trait should be warned that their blood picture resembles iron deficiency and can be misdiagnosed. They should eschew empirical use of iron, yet iron deficiency requiring replacement therapy can develop during pregnancy or from chronic bleeding.

Persons with α thalassemia trait may exhibit mild hypochromia and microcytosis usually without anemia. HbA_2 and HbF levels are normal. Affected individuals usually require only genetic counseling. HbH disease resembles β thalassemia intermedia, with the added complication that the HbH molecule behaves like moderately unstable hemoglobin. Patients with HbH disease should undergo splenectomy if excessive anemia or a transfusion requirement develops. Oxidative drugs should be avoided. Iron overload leading to death can occur in more severely affected patients.

PREVENTION

Antenatal diagnosis of thalassemia syndromes is now widely available. DNA diagnosis is based on polymerase chain reaction (PCR) amplification of fetal DNA, obtained by amniocentesis or chorionic villus biopsy followed by hybridization to allele-specific oligonucleotide probes or direct DNA sequencing.

THALASSEMIC STRUCTURAL VARIANTS

Thalassemic structural variants are characterized by both defective synthesis and abnormal structure.

HEMOGLOBIN LEPORE

Hb Lepore [$\alpha_2(\delta\beta)_2$] arises by an unequal crossover and recombination event that fuses the proximal end of the δ-gene with the distal end of the closely linked β-gene. It is common in the Mediterranean basin. The resulting chromosome contains only the fused δβ gene. The Lepore (δβ) globin is synthesized poorly because the fused gene is under the control of the weak δ-globin promoter. Hb Lepore alleles have a phenotype like β thalassemia, except for the added presence of 2–20% Hb Lepore. Compound heterozygotes for Hb Lepore and a classic β thalassemia allele may also have severe thalassemia.

HEMOGLOBIN E

HbE (i.e., $\alpha_2\beta_2^{26Glu\rightarrow Lys}$) is extremely common in Cambodia, Thailand, and Vietnam. The gene has become far more prevalent in the United States as a result of immigration of Asian persons, especially in California, where HbE is the most common variant detected. HbE is mildly unstable but not enough to affect RBC life span significantly. Heterozygotes resemble individuals with a mild β-thalassemia trait. Homozygotes have somewhat more marked abnormalities but are asymptomatic. Compound heterozygotes for