

Managing Anemia in Pediatric Office Practice: Part 1

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Objectives After completing this article, readers should be able to:

1. Compare and contrast the pathogenesis of iron deficiency anemia in toddlers and older children.
2. Describe the genetic defects resulting in beta-thalassemia and hemoglobin E and differentiate between heterozygous and homozygous defects.
3. Outline the molecular basis for alpha-thalassemia syndromes, including silent carrier, alpha-thalassemia trait, hemoglobin H, and Bart's hemoglobinopathy.
4. Describe the pathogenesis of spherocytes in hereditary spherocytosis and the reasons for the shortened red cell survival.
5. Characterize the risk of "aplastic crisis" in hereditary spherocytosis and the requisite monitoring and management.

Introduction

Children's hematologic and oncologic problems often present initially to the pediatrician. This article provides direction for the diagnosis and office treatment of anemia and guidelines for follow-up and, where appropriate, referral to a subspecialist. Part 1 considers iron deficiency, beta- and alpha-thalassemia trait, and hereditary spherocytosis (Table 1). Part 2 considers sickle cell syndromes, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and transient erythroblastopenia. These topics were proposed by practicing pediatricians in our communities as those of particular concern in their office practices.

Anemia

The traditional measurements of hemoglobin concentration and hematocrit may not be sufficient to determine the presence of anemia of childhood. The "normal values" cited in clinical pathology laboratory reports are unlikely to apply to children. Tables of normal values for children of different ages have been published (Table 2). In general, the hemoglobin is high at birth and falls during the initial 6 to 8 weeks of life to a physiologic nadir before it gradually increases to childhood levels. Patients who suffer from cyanotic congenital heart disease or chronic obstructive pulmonary disease may have values that are considerably higher than children who do not have these problems. These children, therefore, may be anemic when their hemoglobin and hematocrit values are within the normal range for unaffected children. Once the physician has decided that the child's values are two standard deviations below the mean for his or her age group, the cause should be determined.

Iron Deficiency Due To Inadequate Dietary Iron or Chronic Bleeding

History and Physical Examination

The child who has iron deficiency most often presents without symptoms; the condition is detected on routine screening or because of pallor or a low hemoglobin/hematocrit on a blood count performed for another reason. Dietary iron deficiency is most common between the ages of 1 and 3 years as a result of cow milk being a major staple of a child's diet. Cow milk is a very poor source of iron (0.7 mg/L). It is important to obtain a dietary milk history that catalogs precisely the number of bottles or glasses ingested per day, the quantity contained in those vessels, and whether the child drinks additional milk at the time

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Table 1. Red Blood Cell (RBC) Disorders

Disease	Clinical Presentation			
	History	Physical Findings	Laboratory Diagnosis	Treatment
Iron Deficiency	Fatigue Irritability Excess milk intake	Pallor	RBC hypochromic, microcytic Mean cell volume (MCV) ↓ Serum iron ↓ Total iron-binding capacity ↑ % Saturation ↓ Ferritin ↓ Blood in stool or urine Ratio of MCV/RBC > 13	Correct diet Eliminate source of bleeding Ferrous SO ₄ 6 mg/kg per day elemental iron
Alpha- and Beta-Thalassemia Trait	None Pallor Family history	None Pallor	RBC hypochromic, microcytic MCV ↓↓ Basophilic stippling (beta-thalassemia trait) ↑ A ₂ Hemoglobin (Hb) (beta-thalassemia trait) Ratio of MCV/RBC < 13	None to child Test both parents Genetic counseling Avoid iron therapy
Hereditary Spherocytosis	None Abdominal fullness, early satiety Family history History of neonatal jaundice	Pallor, jaundice Splenomegaly	Spherocytes Coombs test negative Reticulocyte % ↑ Osmotic fragility increased Mean corpuscular hemoglobin concentration ↑	No splenectomy if Hb > 10 g/dL (100 g/L) and reticulocyte < 10% Folic acid (0.5 mg qd < 5 y of age; 1.0 mg qd > 5 y of age) Splenectomy and immunizations to pneumococcus, <i>H influenzae</i> , and meningococcus and penicillin prophylaxis

he or she is put to bed or wakes during the night. A milk intake greater than 16 oz/24 h in an 18- to 24-month-old child should raise the question of whether dietary iron intake is adequate. The high satiation value of milk and the milk-induced delay in gastric emptying time interferes with the ingestion of adequate amounts of iron-containing foods, no matter what the parents may

report in a dietary history. Little is found on physical examination beyond pallor; organ enlargement usually is not observed.

Pathogenesis, Signs, and Symptoms

Iron is required not only for the production of hemoglobin, but also for enzymes such as cytochromes that are

Table 2. Normal Hemoglobin and Hematocrit Values*

Age	Hemoglobin (g/dL [g/L])	Hematocrit (%)
Newborn	16.8 (13.7 to 20.1) [168 (137 to 201)]	55 (45 to 65) [0.55 (0.45 to 0.65)]
2 weeks	16.5 (13.0 to 20.0) [165 (130 to 200)]	50 (42 to 66) [0.50 (0.42 to 0.66)]
3 months	12.0 (9.5 to 14.5) [120 (95 to 145)]	36 (31 to 41) [0.36 (0.31 to 0.41)]
6 months to 6 years	12.0 (10.5 to 14.0) [120 (105 to 140)]	37 (33 to 42) [0.37 (0.33 to 0.42)]
7 to 12 years	13.0 (11.0 to 16.0) [130 (110 to 160)]	38 (34 to 40) [0.38 (0.34 to 0.40)]
Adult		
Women	14.0 (12.0 to 16.0) [140 (120 to 160)]	42 (37 to 47) [0.42 (0.37 to 0.47)]
Men	16.0 (14.0 to 18.0) [160 (140 to 180)]	47 (42 to 52) [0.47 (0.42 to 0.52)]

*Results are mean values, with ranges in parentheses. From Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Philadelphia, Pa: WB Saunders Co; 2000:1462.

Table 3. Mean Cell Volume (MCV) and Reticulocyte Percentage in the Diagnosis of Common Anemias

MCV ¹ Normal to Low	MCV ¹ Low	MCV ¹ Normal to High	
		Reticulocytes Increased	Reticulocytes <0.5%
Iron deficiency	Beta-thalassemia trait	Acute bleeding Hereditary spherocytosis	Transient erythroblastopenia of childhood
Lead poisoning Also see Table 6	Alpha-thalassemia trait Also see Table 6	Severe sickle syndromes G6PD Deficiency	Diamond-Blackfan syndrome Parvovirus ²
¹ Normal MCV is 78 to 90 fL/cell			
² The parvovirus syndrome occurs primarily in children who have underlying hemolysis.			

present in all tissues. Thus, iron deficiency is a systemic disease that may be manifested by irritability and developmental delay. Severe dietary iron deficiency may result in trace amounts of blood in the stool because of the lack of cytochrome iron and gastrointestinal mucosal damage or because of milk allergy and enteropathy, but the test for occult blood should be no more than trace positive. The black stools resulting from concurrent iron treatment will not give false-positive results. In children younger than 9 months and older than 3 years of age, dietary iron deficiency is uncommon, and evaluation of the stool for blood loss becomes more important. Rarely, iron may be lost via urinary (intravascular hemolysis) or pulmonary bleeding (pulmonary hemosiderosis).

Laboratory Testing

Use of hemoglobin and hematocrit screening for iron deficiency remains controversial. Screening children between 6 months and 1 year and at 2 and 3 years of age can decrease the risk of the subtle adverse effects of iron deficiency on development. Approximately one third of patients who have iron deficiency anemia have a normal mean cell volume (MCV). Mild anemia of iron deficiency is normocytic and normochromic because the red cell size and hemoglobin fall through the normal range due to lack of iron. It then becomes hypochromic and microcytic, as assessed clinically by a mean corpuscular hemoglobin (MCH) below 25 pg/cell and an MCV below 78 fL/cell on the complete blood count or as reported on the blood film. The role of the MCV and reticulocyte percentage in categorizing the anemias is shown in Table 3. If there is any doubt about the dietary history and the interpretation of the microcytosis and hypochromia, a serum iron and total iron binding capacity (TIBC) can be ordered and a percent saturation calculated. Normal serum iron levels are 22 to 184 mcg/dL (3.4 to

32.9 mcg/dL), TIBC is 100 to 400 mcg/dL (1 to 4 g/L) in infants and 200 to 400 mcg/dL (2 to 4 g/L) in older children, and percent saturation is more than 20%. In iron deficiency, the serum iron concentration is low and the TIBC is high (Table 4). An evaluation of the serum ferritin usually reflects the body iron stores in the absence of inflammatory disease, and it is low in iron deficiency.

Treatment

In a pale, irritable child who has a hypochromic microcytic anemia and a history of greater than 32 oz of whole milk intake per day, the diagnosis almost certainly is related to dietary lack of iron. Many pediatricians would treat such a child with supplemental iron without additional laboratory testing. Because some children may have gastrointestinal bleeding as the etiology of their iron loss, testing with stool occult blood cards on four to five separate occasions is indicated and inexpensive; negative results minimize the risk of this consideration.

The treatment of iron deficiency depends on its etiology. For children who have dietary iron deficiency, the milk in the diet should be reduced promptly to fewer than 16 oz/d. Those children who have gastrointestinal bleeding should undergo imaging and endoscopy and receive appropriate treatment. Iron is administered as iron sulfate (25 mg/mL), and the usual dose for children is 6 mg/kg per day of elemental iron in three divided doses. Older children and adults can be given 325-mg ferrous sulfate tablets that contain 65 mg elemental iron, but they may tolerate only two to three tablets per day (2 to 3 mg/kg per day) because of iron-induced intestinal discomfort. Patients should be treated until the hemoglobin and hematocrit reach the normal range and given at least 1 month of additional treatment to replete the iron stores.

Table 4. Use of Iron Studies in the Differential Diagnosis of Hypochromic Microcytic Anemias

Condition	Serum Iron	Transferrin (Total Iron-binding Capacity)	Iron in Histiocytes	Marrow Sideroblasts	Ferritin
Iron deficiencies (dietary or bleeding)	Low	High	Absent	Absent	Low
Chronic inflammation	Low	Low	Normal or increased	Absent	High
Sideroblastic	Normal or high	Normal	Normal or high	Increased	Normal or high
Normal values*	22 to 184 mcg/dL (3.4 to 32.9 mcmol/L)	Infant, 100 to 400 mcg/dL (1 to 4 g/L) Other, 200 to 400 mcg/dL (2 to 4 g/L)	Present	Present	Newborn 1 month 2 to 5 months 6 months to 15 years Adult Males Adult Females
					25 to 200 ng/mL (25 to 200 mcg/L) 200 to 600 ng/mL (200 to 600 mcg/L) 50 to 200 ng/mL (50 to 200 mcg/L) 7 to 140 ng/mL (7 to 140 mcg/L) 15 to 200 ng/mL (15 to 200 mcg/L) 12 to 150 ng/mL (12 to 150 mcg/L)

*Normal values from Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Philadelphia, Pa: WB Saunders; 2000: Table 726-6.

Indication for Referral

If the response to iron therapy is not adequate within 4 to 8 weeks or if the anemia recurs, there may be persistent bleeding, iron malabsorption, noncompliance, or other causes of a hypochromic and microcytic anemia. The pediatrician may consider evaluating the child for thalassemia trait or lead poisoning. The serum iron and the TIBC are low in chronic inflammatory disease, but the ferritin is elevated, an important distinction (Table 4). In this instance, the child should be evaluated for rheumatologic disorders or chronic infection. The iron-related microcytic anemias, including iron deficiency, chronic inflammatory disease, and sideroblastic anemia, are compared in Table 4. If the diagnosis is not clear, referral to a pediatric hematologist for consideration of less likely conditions, such as sideroblastic anemia, alpha-thalassemia, or combinations of these problems, is appropriate (Table 5). Sideroblastic anemia is a preleukemic condition seen only rarely in children.

Beta-Thalassemia Trait

History and Physical Examination

A family history of anemia or the presence of microcytosis and mild anemia in a patient from the Mediterranean region should alert the pediatrician to the possibility of beta-thalassemia trait. Similar findings in patients from southeast Asia suggest alpha-thalassemia trait, beta-thalassemia trait, or a hemoglobin E syndrome. The blood hemoglobin concentration usually is low-normal, and few or no symptoms may be attributed to it, but chronic fatigue and pallor may be present. The family's name may not suggest the relevant ethnicity, if, for example, the mother has taken the father's last name. It is particularly important to explore both the maternal and paternal sides of the family for a history of anemia because the potential for beta-thalassemia major or E-beta-thalassemia in future children is one of the primary reasons for establishing a diagnosis of beta-thalassemia trait or hemoglobin E in a patient. Aside from mild pallor, little is found on physical examination, and there is no enlargement of the liver or spleen in beta-thalassemia trait. Organomegaly suggests a more severe form of thalassemia.

Pathogenesis, Signs, and Symptoms

Beta-thalassemia trait results from a defect in a single beta-globin gene that results in diminished production of normal beta-globin chains and, hence, di-

Table 5. Hypochromic/Microcytic Anemias

Inherited Impairment of Heme Synthesis

- Beta-thalassemia trait
- Beta-thalassemia major and intermedia
- Alpha-thalassemia trait and hemoglobin H
- Hemoglobin E and Lepore

Acquired Impairment of Heme Synthesis

- Iron deficiency—dietary or bleeding
- Pb—Blocks porphyrin (heme) synthesis
- Chronic inflammation—Iron present in storage histiocytes, but transferrin is low and iron is not transported to erythroblasts, ie, no siderocytes in marrow (see Table 4)
- Sideroblastic—Iron present in storage histiocytes and in mitochondria of sideroblasts, but cannot be incorporated into heme (see Table 4)

minished hemoglobin A and a resultant hypochromic and microcytic anemia. It is inherited as an autosomal recessive trait, and the risk for major thalassemia in a subsequent pregnancy is one in four if both parents are carriers. The diagnosis should be considered in a slightly pale, mildly anemic child of Mediterranean, Asian, or African ethnicity. If the child is between ages 1 and 3 years, dietary iron deficiency also should be considered (Table 5), although failure to respond to therapy for presumptive iron deficiency anemia often leads to a diagnosis of thalassemia trait.

Hemoglobin E is a beta-chain variant ($\alpha_2\beta_2^{26\text{Glu}\rightarrow\text{Lys}}$) that is produced in diminished amounts and, hence, is akin to thalassemia. The hemoglobin E syndromes are summarized in Table 6. Patients who have hemoglobin E trait do not have anemia, but they do have microcytic red blood cells. Homozygous hemoglobin E disease is characterized by mild anemia and severe microcytosis without organomegaly, and E-beta-thalassemia is similar to beta-thalassemia major, with severe anemia, organomegaly from extramedullary hematopoiesis and hemolysis, and a requirement for red blood cell transfusion.

Laboratory Testing

Beta-thalassemia trait is characterized by a mild anemia, with a hemoglobin of 9.5 to 11 g/dL (95 to 110 g/L) in prepubertal children and usually an MCV of less than 80 fL/cell (Table 6). Older children will have values at or just below the normal values for their age and gender. Examination of the blood film often shows marked vari-

ation in size and shape of the red cells, with hypochromia and basophilic stippling. This basophilic staining represents precipitated RNA, which is seen with the standard Wright stain. Basophilic stippling is observed commonly among patients who have lead toxicity and beta-thalassemia trait but not among those who have iron deficiency, making it an important distinguishing feature. The reticulocyte percentage is not significantly elevated. Patients who have beta-thalassemia trait, in contrast to those who have iron deficiency, typically have an increased number of red cells that are smaller than normal, leading to a ratio of the MCV/red cell count per milliliter of less than 13. The ratio in iron deficiency usually is more than 13 (Mentzer index). Quantitative hemoglobin electrophoresis shows an elevation in the percentage of A₂ ($\alpha_2\delta_2$) hemoglobin of greater than 3.5% or an elevation in F ($\alpha_2\gamma_2$) hemoglobin. Electrophoresis should not be performed if there is concurrent iron deficiency because this tends to reduce the level of A₂ hemoglobin and may obscure the diagnosis of thalassemia trait.

The presence of hemoglobin E is detected by hemoglobin electrophoresis. The features of the blood film and red cell indices are shown in Table 6.

Treatment

No specific treatment is required for patients who have beta-thalassemia trait, hemoglobin E trait, or homozygous hemoglobin E. The importance of establishing these diagnoses is to avoid treatment for a deficiency of iron that is not present. It is critical to evaluate both mother and father to ensure that both do not carry a thalassemic gene. If both are affected with beta-thalassemia trait or with beta-thalassemia trait and hemoglobin E, there is a 25% risk of having a child who has a major thalassemia syndrome, a condition that requires chronic transfusion therapy and iron chelation and usually shortens the lifespan.

Indication for Referral

If there is a question about the diagnosis, the genetics, appropriate counseling, or subsequent evaluation, children suspected of having beta-thalassemia or hemoglobin E trait should be referred to a pediatric hematologist. These would include patients whose anemia is more severe than would be expected; they may have a confounding second reason for anemia or they may have beta-thalassemia intermedia, beta-thalassemia major, or E-beta-thalassemia, which present more complex diagnostic and therapeutic problems (Table 6). Beta-thalassemia major usually is recognized during the sec-

Table 6. Laboratory Diagnosis of Thalassemia Syndromes

Hemoglobin (Hb)*	Chain Structure	Normal	Beta-Thalassemia Trait	Beta-Thalassemia Major	Beta ⁺ -Thalassemia Major	E-Trait	EE	E-Beta ⁺ -Thalassemia*
A	Alpha ₂ Beta ₂	>95%	>94%	—	30% to 80% ¹	>65%	—	<10%
F	Alpha ₂ Gamma ₂	<2%	<2%	>95% ¹	20% to 70% ¹	<2%	<10%	<20%
A ₂	Alpha ₂ Delta ₂	<3.5%	3.5% to 7%	1% to 3.5%	1% to 3.5%	<3.5%	**	5%
E	Alpha ₂ Beta _E	—	—	—	—	<35%	>90%**	>50%
Hb level	—	Normal	9.5 to 11 g/dL (95 to 110 g/L)	2 to 3 g/dL ¹ (20 to 30 g/L)	3 to 9 g/dL ¹ (30 to 90 g/L)	>12 g/dL (>120 g/L)	>10 g/dL (>100 g/L)	2 to 7 g/dL (20 to 70 g/L)
MCV (fL/cell)	—	78 to 90	<80	<75 ¹	<75 ¹	<80	<65	<75
Morphology	—	Normal	Hypochromia and microcytosis Variation in size and shape Basophilic stippling	Marked hypochromia and microcytosis Variation in size and shape Nucleated RBC	Marked hypochromia and microcytosis Variation in size and shape Nucleated RBC	Hypochromia and microcytosis Target cells	Microcytosis Target cells Coarse basophilic stippling	Marked hypochromia and microcytosis Variation in size and shape Nucleated RBC Target cells

¹The hemoglobin F, hemoglobin level, and MCV values for beta-thalassemia are approximations because many cases are reported after transfusion. In current practice, the diagnosis may be suspected from a newborn screen and established when the hemoglobin falls below 7 to 8 g/dL (70 to 80 g/L). Currently, patients who have major thalassemia are transfused prior to their hemoglobin falling as low as 2 to 3 g/dL (20 to 30 g/L).

*Values at time of diagnosis at 6 months to 2 years, before transfusion. From Weatherall DJ, Clegg JB. *The Thalassemia Syndromes*. 4th ed. New York, NY: Blackwell Scientific Publishing; 2001.

**Hgb E comigrates with A₂.
MCV = mean cell volume, RBC = red blood cell

and half of the first year of life when gamma-chain and fetal hemoglobin (alpha₂gamma₂) production fall. The child becomes progressively more anemic because there is little or no production of beta-chain or hemoglobin A (alpha₂beta₂). The severe hypochromic microcytic anemia requiring transfusion and the resultant enlargement of the liver and spleen because of extramedullary hematopoiesis suggest the diagnosis of thalassemia major. Other causes of hypochromic microcytic anemias are shown in Table 5.

Alpha-Thalassemias History and Physical Examination

Patients who have alpha-thalassemia trait (two-gene deletion alpha-thalassemia) usually are asymptomatic. Alpha-thalassemia trait should be considered when beta-thalassemia trait is suspected, but the A₂ and F hemoglobin levels are normal. It is seen most often in Asian populations but also may occur in persons of Mediterranean and African descent. Patients who have alpha-thalassemia trait have normal physical examination findings because anemia usually is not present. Only with more severe alpha-thalassemia syndromes, such as hemoglobin H disease, is there moderate anemia, usually characterized by a hemoglobin of 7 to 10 g/dL (70 to 100 g/L) and splenomegaly.

Pathogenesis, Signs, and Symptoms

Alpha-thalassemia trait should be suspected in patients of the appropriate ethnic background who have red cells with a decreased MCV, do not have iron deficiency, and present a normal hemoglobin A₂ by quantitative electrophoresis. Alpha-thalassemia trait results from the deletion of two alpha-globin genes, which impairs the production of glo-

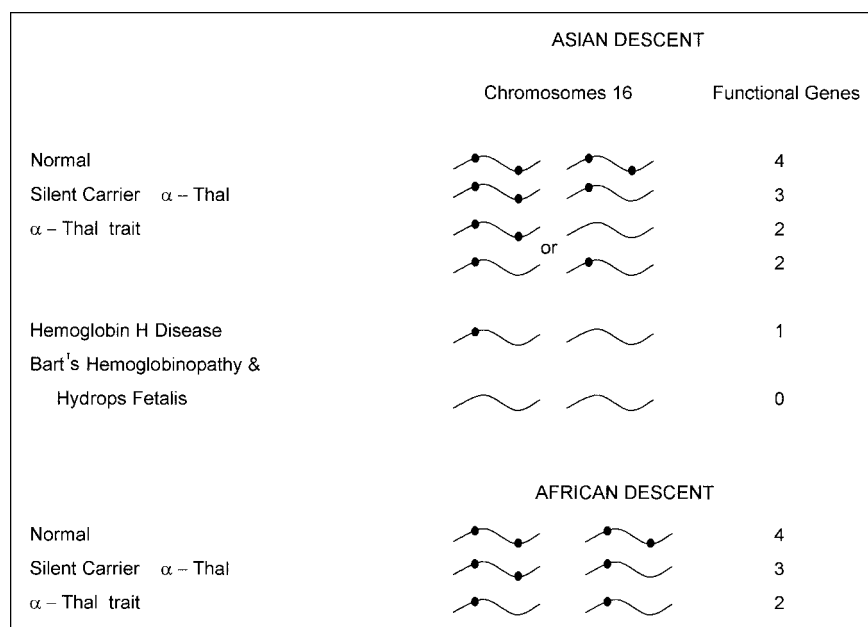


Figure 1. Genetic differences in alpha-thalassemia syndromes.

bin, but does not increase A_2 hemoglobin. Alpha-thalassemia differs between the Asian and African populations in that the two defective genes do not occur on the same chromosome in African-Americans (Fig. 1). Thus, only the normal, silent carriers, and the alpha-thalassemia trait phenotypes are seen.

The pathogenesis of the alpha-thalassemia syndromes involves a four-gene system, as shown in Fig. 1. Unaffected people have four normal genes, two on each chromosome 16. The severity of the clinical syndrome depends on the number of genes that are defective. If one gene is inactive, there is no clinical phenotype, and the patient is designated a silent carrier of alpha-thalassemia. A two-gene deletion results in alpha-thalassemia trait that may occur either from one defective gene on each chromosome, as in African or Asian populations, or from two defective genes on a single chromosome, as in Asian populations. These patients have red blood cell microcytosis with little or no anemia. Three- and four-gene deletions occur almost exclusively in the Asian population. Three defective genes result in hemoglobin H disease. Hemoglobin H is composed of a tetrad of beta-chains because of the paucity of available alpha-chains, and it is characterized by a chronic hemolytic anemia with splenomegaly. Four defective genes preclude assembly of hemoglobin F or hemoglobin A, which results in a tetrad of four gamma genes in the newborn, termed Bart's hemoglobin. Bart's hemoglobinopathy produces a

catastrophic anemia, hydrops fetalis, and fetal or neonatal loss.

Laboratory Testing

Alpha-thalassemia usually is diagnosed from the family history and the absence of beta-thalassemia trait or iron deficiency anemia. The hemoglobin and hematocrit usually are within the normal range, but a marked microcytosis of less than 70 fL/cell is present. Patients who have alpha-thalassemia trait do not have increased levels of hemoglobin A_2 . There is no convenient laboratory test for diagnosing the alpha-thalassemia syndromes. Research techniques can detect the amount of alpha- and beta-globin chain production in a patient's reticulocytes. Such studies indicate that the beta/alpha production ratio is greater than 1 if alpha-chain

synthesis is impaired, as in alpha-thalassemia trait (mean ratio, 1.3) or hemoglobin H disease (mean ratio, 2.6). Molecular techniques can detect the defective or absent alpha genes, and these will become more readily available for clinical diagnosis.

Treatment

No treatment is necessary for patients who have alpha-thalassemia trait. Patients who have hemoglobin H disease may require the administration of folic acid, transfusion therapy, and in rare instances of hypersplenism, splenectomy. Bart's hemoglobinopathy usually results in neonatal death. However, patients rarely have been salvaged with intrauterine transfusions and subsequent stem cell transplantation, which should be considered the treatment of choice if a donor is available.

Indication for Referral

The suspicion of alpha-thalassemia trait in patients of Asian descent warrants consultation with a pediatric hematologist to make a definitive diagnosis and to provide a risk assessment for the potential of having a child who has Bart's hemoglobinopathy. Appropriate screening of the parents of an affected Asian child to determine if both are carriers is indicated. Referral may be helpful in excluding other hypochromic and microcytic anemias in patients of African descent.

Hereditary Spherocytosis

History and Physical Examination

The severity of hereditary spherocytosis varies greatly, but it frequently causes hemolytic disease and severe hyperbilirubinemia in the newborn. Alternatively, some children remain asymptomatic and are detected because they have splenomegaly or because a mild anemia is found on a routine examination. The history also may reveal the presence of jaundice, anemia, or a familial history of splenectomy, gallbladder disease, or hereditary spherocytosis. Those who have severe disease develop pallor, fatigue, jaundice, and exercise intolerance during childhood. Because of the increased red cell turnover, affected children may develop cholelithiasis, and they are susceptible to aplastic crisis, primarily as a result of parvovirus infection. The marrow failure in an aplastic crisis may result in severe, life-threatening anemia.

Approximately 75% of patients have a positive family history. The remaining 25% may represent new mutations or occasionally recessive inheritance or nonpaternity. Physical examination may reveal pallor, jaundice, and splenomegaly.

Pathogenesis, Signs, and Symptoms

Hereditary spherocytosis results from abnormalities in red cell membrane proteins such as spectrin, ankyrin, or protein band 3. The molecular basis for many of these defects has been defined. Physiologically, membrane is lost, resulting in a decrease in membrane surface area in relation to red cell volume. As a consequence, there is a change toward a spherical shape, which permits the cell to be destroyed prematurely in the spleen.

The diagnosis of hereditary spherocytosis also is suggested by asymptomatic splenomegaly. It is worthwhile to examine the child's parents if they are available because splenomegaly in a parent makes the diagnosis of hereditary spherocytosis likely even before laboratory data are obtained. Anemia may be present, but increased red cell production is reflected in an elevated reticulocyte percentage. Parvovirus and other viruses can suppress the reticulocytosis and cause an aplastic crisis with an acute profound anemia. The chronic hemolysis may result in cholelithiasis and cholecystitis in the first decade of life.

Hereditary spherocytosis is the most common of the hereditary red cell membrane disorders and usually is inherited as an autosomal dominant trait. It should be considered early in the differential diagnosis of neonatal jaundice along with hemolytic disease of the newborn resulting from maternal antibodies to ABO antigens that also may cause spherocytosis. In older children, hereditary spherocytosis should be distinguished from immu-

Table 7. Causes of Spherocytosis

Hereditary Spherocytosis

Immuno-hemolytic Anemia

- Isoimmune: ABO incompatibility
- Autoimmune warm antibody
 - Idiopathic
 - Secondary to collagen vascular disease, viral illness, drugs, lymphoma, hypogammaglobulinemia
- Autoimmune cold antibody
 - Idiopathic
 - Secondary to lymphoma, *Mycoplasma* infection

Membrane Damage

- Clostridial toxin
- Severe burns
- Wilson disease (Cu^{++})

nohemolytic anemias; both disorders feature large numbers of spherocytic red cells on the blood film. The latter is confirmed by the presence of a positive antiglobulin (Coombs) test. Other causes of spherocytosis are listed in Table 7.

Laboratory Testing

A complete blood count and reticulocyte percentage may reveal anemia with a reticulocytosis that reflects increased red cell production in the absence of bleeding. A family history, splenomegaly, reticulocytosis, spherocytes present on the blood film, and an increased mean corpuscular hemoglobin concentration strongly suggest the diagnosis of hereditary spherocytosis. The presence of similar findings in a parent confirms this diagnosis, and no further testing is necessary. An antiglobulin test is required to eliminate immuno-hemolytic anemia from the differential diagnosis. The osmotic fragility test (Fig. 2) can detect spherocytes if there is uncertainty about their presence on the blood film, but it is not specific for the diagnosis of hereditary spherocytosis. In this test, spherocytic red cells hemolyze more readily in hypotonic solutions, particularly if they are incubated in the absence of added glucose overnight. Specific protein abnormalities in spectrin, ankyrin, or band 3 can be defined in research laboratories, as can the various molecular abnormalities.

Treatment

The pediatrician needs to establish the baseline for the patient's hemoglobin, hematocrit, and reticulocyte percentage. These measurements must be repeated in the

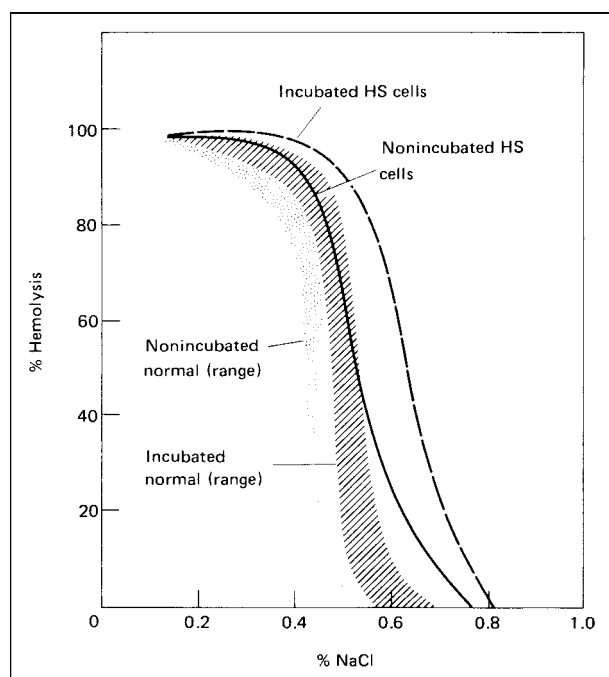


Figure 2. Osmotic fragility of red cells in hereditary spherocytosis (HS). Reproduced from Reich PR, ed. *Hematology*. 2nd ed. Boston, Mass: Little Brown and Company; 1984.

presence of any febrile illness to ensure that the reticulocyte percentage has not fallen as a result of parvovirus or other viruses that can precipitate an aplastic crisis and a life-threatening fall in hemoglobin and hematocrit concentrations. The management of an aplastic crisis requires consultation with a hematologist. The spherocytes in hereditary spherocytosis are destroyed almost exclusively in the spleen, and splenectomy eliminates most of the hemolysis in this disorder. Splenectomy is recommended (after age 5 y) if the patient cannot maintain a hemoglobin of 10 g/dL (100 g/L) or a reticulocyte percentage less than 10% or if he or she has had an aplastic crisis. Folic acid (0.5 mg for those younger than age 5 y and 1 mg/24 h for those older than age 5 y) should be administered to prevent secondary folic acid deficiency. Transfusion therapy may be used in children younger than 2 years of age who have severe disease. Splenectomy is delayed to beyond 5 to 6 years, if possible, to avoid the heightened risk of postsplenectomy sepsis, although it may be performed earlier (between 2 and 5 y) in severe disease. Immunization with *Haemophilus influenzae*, *Streptococcus pneumoniae* (multivalent (23PS)), and *Neisseria meningitidis* vaccines is re-

quired prior to splenectomy, and penicillin prophylaxis is required indefinitely thereafter.

Indication for Referral

It is useful to consult a pediatric hematologist at the earliest possible time when hereditary spherocytosis is the potential diagnosis, so that all of the alternative diagnoses (Table 7) can be considered; the genetics of the disease discussed with the parents; and the issues relating to aplastic crises, the risk of cholelithiasis, potential splenic injury, and the need and timing for splenectomy reviewed. Once a management plan is established (either after birth or later), an annual visit to a hematologist is recommended for regular assessment of the need for splenectomy. The pediatrician needs to monitor the child's reticulocyte percentage closely when there is a febrile illness. A reticulocyte percentage well below the baseline heralds a marked decrease in hemoglobin and hematocrit. The child who has this type of aplastic crisis should be referred to the hematologist.

Suggested Reading

- Beutler E, Lichtman MA, Coller BS, Coller TJ, Seligsohn U, eds. *Williams Hematology*. 6th ed. New York, NY: McGraw-Hill; 2001
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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. During a health supervision visit, laboratory results document a hemoglobin of 11.0 g/dL (110 g/L) in a 12-month-old girl. Other information provided by the automated cell counter includes a mean cell volume of 80 fL, white blood cell count of $10.6 \times 10^3/\text{mCL}$ ($10.6 \times 10^9/\text{L}$), and a platelet count of $350 \times 10^3/\text{mCL}$ ($350 \times 10^9/\text{L}$). The *most* likely explanation for these findings is:
 - A. Alpha-thalassemia trait.
 - B. Intercurrent viral illness.
 - C. Mild iron deficiency anemia.
 - D. Normal findings for age.
 - E. Transient erythroblastopenia of childhood.
2. A 14-month-old girl born to parents who are from Greece has a hemoglobin of 9.6 g/dL (960 g/L) and a mean cell volume of 62 fL. After a trial of iron failed to increase the hemoglobin concentration, a quantitative hemoglobin electrophoresis reveals an elevation of hemoglobin A₂ and F. The *most* important next step is to:
 - A. Avoid prolonged and unnecessary iron therapy.
 - B. Exclude the possibility of concomitant iron deficiency.
 - C. Exclude the possibility of alpha-thalassemia minor.
 - D. Exclude the possibility of beta-thalassemia major.
 - E. Provide family testing and genetic counseling, if appropriate.
3. The 6-year-old son of a woman who has hereditary spherocytosis develops pallor following an upper respiratory tract infection. Testing reveals a hemoglobin of 8.3 g/dL (830 g/L), an elevated mean corpuscular hemoglobin concentration (MCHC) of 36.5%, a serum bilirubin of 2.1 mg/dL (35.9 μmol/L), and the presence of spherocytes in the peripheral blood smear. (The hemoglobin is stable the next day, but rises to 10.9 g/dL [109 g/L] in 3 weeks, accompanied by a serum bilirubin of 1.1 mg/dL [18.8 μmol/L].) Of the following, the *most* important next step in the management of this child is to:
 - A. Determine the reticulocyte count and observe the child for possible aplastic crisis.
 - B. Perform a direct Coombs test.
 - C. Perform an osmotic fragility test.
 - D. Schedule elective splenectomy.
 - E. Transfuse with packed red cells.
4. A 12-month-old girl is found to have a hemoglobin of 11.0 g/dL (110 g/L) during a health supervision visit. Other information provided by the automated cell counter includes a mean cell volume of 66 fL, red cell count of $5.3 \times 10^6/\text{mCL}$ ($53. \times 10^{12}/\text{L}$), and normal white blood cell and platelet counts. Results of quantitative hemoglobin electrophoresis are normal. The girl has no siblings. Genetic counseling is *most* important if the family is of which ethnic group?
 - A. Asian.
 - B. African.
 - C. Greek.
 - D. Native American.
 - E. Northern European.