Hereditary Spherocytosis

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Hereditary Spherocytosis

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Objectives

After completing this article, readers should be able to:

1. Recognize the primary clinical features of hereditary spherocytosis (HS).
2. Identify the blood tests used to diagnose HS.
3. Recognize the signs of an aplastic crisis due to parvovirus B19.
4. Recognize the signs of a hemolytic crisis.
5. Describe the indications for splenectomy in HS.
6. Delineate the risk of postsplenectomy sepsis in patients who have HS.
7. Understand the importance of presplenectomy vaccination and postsplenectomy antibiotic prophylaxis in patients who have HS.
8. Identify the primary long-term complication of HS.

Introduction

Hereditary spherocytosis (HS) is the most common red cell membrane disorder. Morphologically, spherocytes are rounded red cells that have lost the ability to change shape. Chronic hemolysis is the hallmark of HS. In most individuals, the condition is mild and requires no specific therapy. In severe cases, it results in severe anemia, splenomegaly, and jaundice. Splenectomy sometimes is recommended as therapy for severe cases and can result in amelioration of the disease. Patients who have undergone splenectomy are at increased risk for infections with encapsulated bacteria. Appropriate counseling and management of fever are essential to minimize the risk of sepsis in postsplenectomy patients.

Epidemiology and Genetics

HS was described initially in 1871. It is found in increased numbers among persons of northern European descent. The incidence of HS is estimated to be 1 in 5,000 in the United States. Most cases are inherited in an autosomal dominant fashion. Approximately 25% of cases are discovered in persons who have no family history of HS; these cases may represent spontaneous mutations or recessive forms of the disease.

Over the past several decades, basic science researchers have discovered that abnormalities in several of the red cell membrane proteins (Fig. 1) can lead to the clinical manifestations typical of HS. In European and American patients, ankyrin-1 mutations are the major cause of dominant and recessive HS in approximately 35% to 65% of affected patients, and 15% to 25% of patients have band 3 mutations. Japanese patients have mutations primarily in band 3, protein 4.2 genes, or both and have fewer ankyrin gene mutations. In pedigrees that have a dominant defect, affected family members tend to have similar degrees of hemolysis and clinical severity.

Pathogenesis

Regardless of the molecular basis for a case of HS, the common denominator of spectrin deficiency results in an unstable red cell membrane. Disruptions of ankyrin, band 3, or the other structural proteins lead to common secondary defects in spectrin assembly, resulting in an unstable red cell membrane. Lipids are lost from the bilayer as microvesicles. As the red cell progressively loses surface area, it changes from a biconcave disc to a sphere (Fig. 2). As a result of this shape change, the red cells lose their ability to circulate freely through narrow capillaries in the body. The resulting spherocytes become trapped in the spleen as

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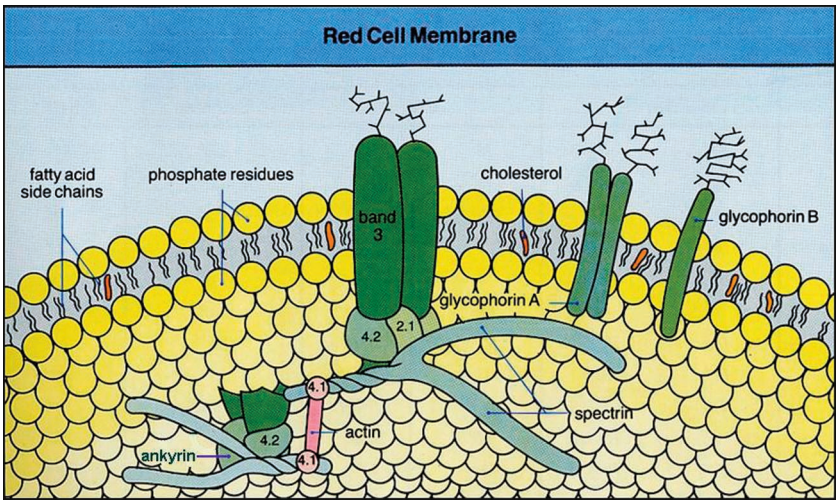

Figure 1. Major protein components of the red cell membrane include actin, spectrin, and band 3 protein.

they course through the sinuses, and the red cells are engulfed by macrophages. Hemolysis causes elevations of unconjugated bilirubin and the development of gallstones.

Clinical Aspects

Signs and Symptoms

Due to the heterogenous nature of the biochemical defects underlying HS, clinical manifestations may vary (Table 1). HS can present soon after birth. It should be suspected in the infant in whom jaundice presents in the first 24 hours after birth or in whom jaundice persists beyond the first postnatal week. In the first few postnatal months, anemia can develop in children who do not mount an adequate reticulocyte response. In later childhood, HS can present with anemia, jaundice, and splenomegaly. Affected patients may have mild, moderate, or severe anemia. Patients who have mild anemia due to HS may have normal hemoglobin values (11 to 15 g/dL [110 to 150 g/L]) and mildly elevated reticulocyte counts (<5% [0.05]). Patients who have moderate anemia may have hemoglobin concentrations of 8 to 12 g/dL (80 to 120 g/L). Severe HS is characterized by severe anemia, with hemoglobin concentrations of 6 to 8 g/dL (60 to 80 g/L) and reticulocyte counts often exceeding 10% (0.10). Children who have moderate-to-severe anemia may have poor exercise tolerance, poor growth, and academic difficulties. Older individuals develop bilirubin stones and may present with cholecystitis.

Laboratory Evaluation

Laboratory testing is helpful in both establishing the diagnosis of HS and classifying the severity of illness. In the initial evaluation, it often is useful to study relatives as well as individual patients. Most patients have a positive family history of HS.

The peripheral blood smear in HS shows numerous spherocytes that appear as red cells that do not have any central pallor and are smaller than usual. Larger bluish cells (polychromasia) also may be seen. The complete blood count (CBC) and reticulocyte count reveal a low hemoglobin concentration and elevated reticulocyte count. The mean corpuscular hemoglobin concentration usually is high at greater than 35 g/dL (350 g/L). The mean corpuscular volume may be low or high if there is substantial reticulocytosis.

The test of osmotic fragility can be useful in establishing the diagnosis of HS. The test is based on the principle that red cells swell and rupture when incubated in hypotonic solutions. Because spherocytes have reduced cell membranes, they swell at higher concentrations of saline than do normal red cells. The test is performed at a range of hypotonic saline concentrations, with the percent lysis calculated and data plotted graphically and compared with control red cells. The results for a patient whose spherocytes have increased osmotic fragility demonstrate a curve that lies to the right of normal (Fig. 3). The sensitivity of the osmotic fragility test is improved if the

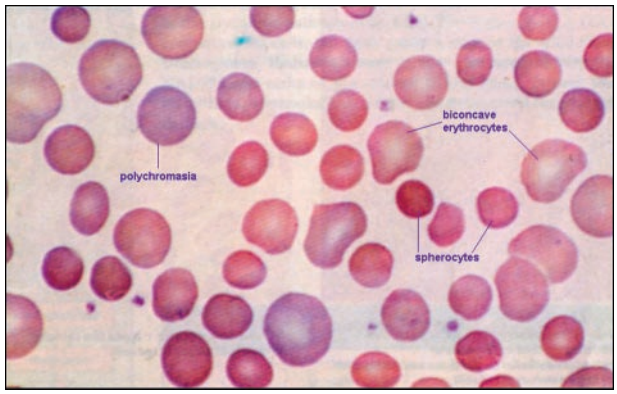

Figure 2. Comparison of normal biconcave erythrocytes and a spherocyte lacking central pallor.

Table 1. Cardinal Signs of Hereditary Spherocytosis

- Anemia
- Jaundice
- Splenomegaly

red cells are allowed to incubate for 24 hours (ie, incubated osmotic fragility). A limitation of the test is that reticulocytes do not have increased fragility. Patients who have HS and very high reticulocyte counts, therefore, may not have increased osmotic fragility. In addition, normal ranges for osmotic fragility are different in infants. For this reason, it is recommended to wait until the infant is 1 year of age before performing this assay to evaluate for HS.

Other test results that support the diagnosis of HS include elevated unconjugated bilirubin, elevated lactic dehydrogenase, and low haptoglobin levels. However, these findings are associated with any case of hemolysis and are not specific for HS.

Differential Diagnosis

In the absence of an informative family history, it can be difficult to be certain of the diagnosis of HS, especially in the nursery, where infants may suffer from many other conditions. Spherocytes often are seen in cases of immune-mediated hemolysis, such as in ABO incompatibility. In this situation, the results of a Coombs test should be positive. Other conditions associated with spherocytes include burns, venom intoxication, pyropoikilocytosis, and unstable hemoglobin variants. In unusual cases of unexplained hemolysis, analysis of red cell membrane proteins by electrophoresis and genetic analysis may be needed to establish a diagnosis. This most often is performed after consultation with a hematologist and reference laboratories.

Management of Complications of HS

General Management

Persons who have mild or moderate anemia due to HS may not require any specific therapy. An annual physical examination to document growth and development of the child is essential. Special attention should be paid to documenting the size of the spleen and educating family members about the diagnosis. Genetic counseling should be offered. A CBC and reticulocyte count should be performed. If the reticulocyte count is not in response to the ongoing hemolysis, the patient may be developing iron or folic acid deficiency. These also may be checked annually and supplementation provided if needed.

The birth of a child to a family in which HS is documented represents a unique opportunity to prevent complications of severe jaundice and anemia. Attention to the hemoglobin and bilirubin levels is paramount. If they are abnormal, the child may be affected by HS and require close follow-up. Obtaining serial hemoglobin levels and reticulocyte counts may be helpful. Studies indicate that severe anemia requiring transfusion develops in the first postnatal month in most cases of severe HS. Referral to a hematologist should be made if anemia develops in the neonate.

Red Cell Tranfusions

Transfusions usually are not required for patients who have the dominant form of HS. Specific indications (Table 2) for transfusion include exacerbation of anemia due to blood loss (such as related to trauma or surgery), hypersplenism, and infection with parvovirus B19. Hy-

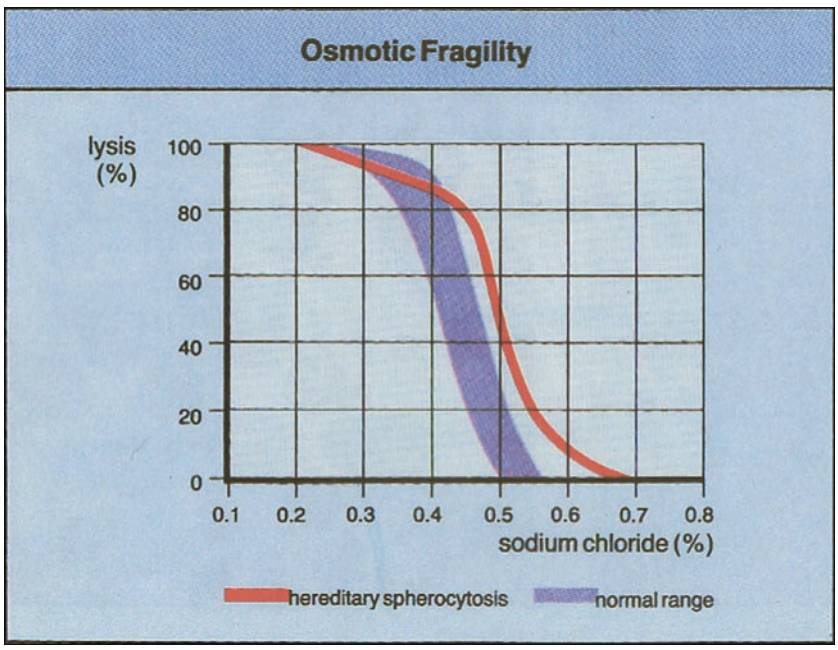

Figure 3. Osmotic fragility of a spherocyte in HS is increased compared with normal erythrocytes.

Table 2. Possible Indications for Transfusion in Hereditary Spherocytosis

- Severe anemia (hemoglobin <8 g/dL [80 g/L])
- Hypoplastic crisis due to parvovirus B19 infection
- Hypersplenism
- Poor growth
- Chronic fatigue

persplenism may occur in patients who have any infection. It is believed that the spleen enlarges in response to an intercurrent infection, with spherocytes consumed as innocent bystanders. In contrast, parvovirus B19 specifically infects red cell progenitors in the bone marrow and induces a 1- to 2-week period of red cell aplasia. This is reflected by a severe drop in the reticulocyte count. Patients who have HS and ongoing baseline hemolysis develop severe anemia with symptoms of heart failure if not transfused during such an episode. For patients who have hemolytic anemia and depend on a high reticulocyte count, a decrease in the reticulocyte count causes a reduction in hemoglobin concentrations.

Splenectomy

Patients who have HS that is characterized by severe hemolysis and severe anemia often are counseled to undergo splenectomy. Red cell survival improves dramatically after splenectomy. Anemia and jaundice also improve significantly. Absolute indications for splenectomy remain controversial (Table 3). They include severe anemia requiring transfusion, growth failure, chronic fatigue, and signs of extramedullary hematopoiesis (frontal bossing). A patient who has an enlarged spleen and is interested in participating in contact sports may warrant splenectomy.

A well-recognized risk of splenectomy is the increased chance for invasive infections with encapsulated bacteria. The decision to recommend splenectomy should not be made lightly. The risk for infection is highest in the months after surgery, but persists for life. It carries an estimated mortality rate of 1 per 1,000 patient-years. It is higher for children undergoing splenectomy at a younger age. For this reason, splenectomy usually is not recommended for children younger than 5 years of age. The rate of infection is lowered but not eliminated by prophylactic antibiotics such as penicillin. Referrals to the pediatric hematologist/oncologist and pediatric surgeon should be made prior to splenectomy.

Table 3. Indications for Splenectomy for Hereditary Spherocytosis

- Severe anemia (hemoglobin <8 g/dL [80 g/L])
- Poor growth
- Chronic fatigue
- Extramedullary hematopoiesis

In the past decade, pediatric surgical teams have gained more experience with laparoscopic procedures. Advantages of laparoscopic splenectomy over conventional splenectomy include less pain and discomfort, brief hospital stays, and prompt return to normal activity. Disadvantages include a limited ability to search the abdomen for accessory spleens that may continue to cause ongoing hemolysis and necessitate a second surgical procedure. In addition, a very large spleen may be difficult to remove laparoscopically. At present, the operative approach is at the discretion of the surgeon.

A possible surgical option for the youngest patients who have severe hemolysis and HS is a partial splenectomy. Partial splenectomy has been shown to decrease the rate of hemolysis and may decrease the need for transfusion. One of the advantages is that the phagocytic function of the spleen may be maintained by the splenic remnant. It is postulated that the rate of invasive bacterial infections may not be as high as with patients who undergo total splenectomies and that partial splenectomies pose less of a risk in the youngest children. It may be considered an attractive alternative to total splenectomy by surgical teams who have appropriate expertise.

In planning for splenectomy, it is crucial to vaccinate the child against *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Neisseria meningitides* several weeks before surgery. It is equally important to counsel caregivers about the need for urgent evaluation of fever after splenectomy and the requirement for indefinite use of penicillin prophylaxis. Postsplenectomy, a patient who has HS should be examined by a physician if he or she develops a temperature greater than 101.3°F (38.5°C). At that time, a CBC and blood culture should be obtained, and an intravenous antibiotic such as ceftriaxone, which has adequate coverage for *S pneumoniae*, should be administered. With older patients, the appropriate duration of antibiotic prophylaxis is unclear. Most experts recommend continuing prophylaxis throughout adolescence. Thereafter, patients are given a supply of antibiotic to take at home if fever develops and are instructed to be examined by a physician immediately.

Cholecystectomy

Chronic hemolysis in HS often leads to the development of gallstones in the teenage years. Coinheritance of the Gilbert syndrome is associated with a fivefold increased risk of developing stones. Some experts recommend ultrasonographic screening for gallstones every few years after age 5. Cholecystectomy is recommended for painful, symptomatic gallstones or bile duct obstruction. It also may be performed at the time of splenectomy if gallstones are found preoperatively on ultrasonography.

Prognosis

In most cases of HS, the hemolytic anemia is not severe and is well compensated by a healthy bone marrow. Patients requiring splenectomy experience improvement in their anemia and jaundice, but do remain at increased risk for infection with encapsulated bacteria. Older individuals are at risk for gallstones and may require cholecystectomy.

ACKNOWLEDGMENTS

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Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

9. The parents of a 4-year-old boy who has known hereditary spherocytosis ask you about surgical options for management of the disease. Which of the following is the *most* accurate response?

   A. Cholecystectomy should be performed immediately if gallstones are identified.
   B. Laproscopic splenectomy carries too high a risk for use in children younger than 10 years of age.
   C. Pneumococcal vaccination is limited to children younger than 5 years of age prior to splenectomy.
   D. Splenectomy almost always improves the anemia dramatically.
   E. The risk of infection following splenectomy varies little with the age of the patient.

10. A 4-year-old boy presents with mild pallor and icterus following a viral infection and is found to have hereditary spherocytosis. He is a single child. The parents want to know more about the genetics of the disease. Which of the following *most* accurately reflects the genetics of this disease?

    A. As many as 25% of patients have no family history of the disease.
    B. Defects in protein 4.2 genes are most frequent in those of northern European descent.
    C. Hereditary spherocytosis usually is inherited in an autosomal recessive fashion.
    D. The disease is most frequent among those of Asian descent.
    E. Within a family, the severity of disease can vary considerably.

11. A previously well 8-year-old girl develops abrupt severe pallor following an upper respiratory tract infection. She is in no acute distress, but she is icteric and obviously pale. Her spleen is palpable 3 cm below the left costal margin. Laboratory findings include: hemoglobin, 3.8 g/dL (38 g/L); mean corpuscular volume, 86 fL; white blood cell count, 13.1×10^3/mcL (13.1×10^9/L); and platelet count, 440×10^3/mcL (440×10^9/L). The blood smear reveals polychromasia and moderate spherocytosis. Of the following, the *most* appropriate laboratory test to obtain is a:

    A. Direct bilirubin.
    B. Direct Coombs.
    C. Haptoglobin.
    D. Indirect bilirubin.
    E. Lactate dehydrogenase.

12. Most children who have hereditary spherocytosis do not require blood transfusions. When necessary, the *most* common indication for red cell transfusions in these children is:

    A. Concomitant folate deficiency.
    B. Hypersplenism.
    C. Ongoing monthly transfusions for severe anemia.
    D. Parvovirus B19-induced aplastic crisis.
    E. Preoperative transfusion.

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