

HEREDITARY SPHEROCYTOSIS

A Guide for the Primary Care Physician

INTRODUCTION, INCIDENCE, AND PATHOPHYSIOLOGY:

Hereditary spherocytosis (HS) is the most common congenital hemolytic anemia occurring in Caucasians. It is also seen frequently in Hispanics but is uncommon in African Americans. Its estimated frequency in the general population is about 1 in 2,000 to 5,000 persons. HS is usually inherited as an autosomal dominant trait, with variable penetrance and a high spontaneous mutation rate. In particularly severe cases an autosomal recessive inheritance pattern may exist, with affected individuals representing homozygotes or compound heterozygotes (with both parents mildly affected carriers). HS is a disorder of the red blood cell membrane. The basic defect is characterized in all cases but is usually a unique mutation resulting in qualitative or quantitative deficiency of structural proteins of the erythrocyte membrane structural protein, such as band 3, glycophorin, ankyrin, or spectrin. The cells lose surface membrane as a result and become spheroidal. These abnormal red blood cells are removed prematurely from the circulation by the spleen.

CLINICAL MANIFESTATIONS:

Patients with HS generally have a mild to moderately severe chronic hemolytic anemia. Many patients are asymptomatic, with only slightly reduced hemoglobin values, rare clinical problems, and a normal physical examination except for slight splenomegaly. Other children, however, have fatigue, decreased exercise tolerance, periodic jaundice, and episodes of more severe anemia (particularly during or following viral infections) which require monitoring and occasionally blood transfusions.

PRESENTATION:

The following are the most common clinical presentations of HS:

1. Identification on the basis of a positive family history: Since the condition is usually autosomal dominant, there is a 50-50 chance that the offspring of an affected parent will have the disorder. Therefore, many patients (particularly newborn infants and young children) are identified on the basis of studies prompted by a family history of HS. Sometimes a specific diagnosis has not previously been made in the parents and other relatives. Family members may have had their chronic anemia “cured” by splenectomy. They may also have a history of gallstones, cholecystectomy, jaundice, or other evidence of a chronic

familial hemolytic anemia. Sometimes there may be an incorrect diagnosis of Gilbert disease in family members.

2. Neonatal hyperbilirubinemia (\pm anemia): Approximately 50% of neonates with hereditary spherocytosis have jaundice of enough severity to require phototherapy or even exchange transfusion. Spherocytes are noted on the blood smear. The differential diagnosis includes other causes of neonatal jaundice, in particular ABO incompatibility (in which spherocytes are a common finding). Although affected patients are usually not severely anemic in the immediate neonatal period, during the first several months of life symptomatic anemia may require one or two blood transfusions. The anemia usually becomes less severe by 4-5 months of age.
3. Mild anemia unresponsive to iron therapy: A common clinical presentation is an infant or young child who has mild anemia (see below for hematologic values) that is unresponsive to iron. A careful review indicates no history consistent with iron deficiency, a normal MCV, sometimes an elevated MCHC, elevated reticulocyte count, and/or spherocytes on the blood smear. The diagnosis of HS should be considered in any Caucasian or Hispanic child with chronic anemia who has an elevated reticulocyte count. Sometimes spherocytes on the blood smear are not obvious to the untrained eye.
4. Asymptomatic splenomegaly, jaundice, or gallstones: Previously well children or adolescents – with or without a history of documented anemia – may sometimes be found to have splenomegaly, jaundice, or gallstones of otherwise uncertain etiology. The presence of any of these three clinical findings should prompt an investigation for HS.
5. Severe anemia (requiring blood transfusion therapy) resulting from an aplastic or hyperhemolytic crisis: Occasionally previously undiagnosed patients present with severe or even life-threatening anemia resulting from a parvovirus B19 induced aplastic crisis or hyperhemolytic episode (see below). The presence of spherocytes on the blood smear (and often – when a detailed history is taken – other features of the disease) prompts consideration of the correct diagnosis.

DIAGNOSIS

The diagnosis of HS can be made when there is a consistent history (outlined above) and there are numerous microspherocytes on a blood smear. In some children the hemoglobin concentration is in the normal range. In most children the anemia is only mild, with hemoglobin values between 9 and 11.5 gm/dl. Even though the spherocytes exhibit decreased diameter, their volume (i.e., MCV) is normal. The MCHC may be slightly elevated (35 to 37 gm/dl) in some cases. The reticulocyte count is nearly always elevated in the 3 – 15% range. WBC and platelet counts are normal.

The diagnosis is strengthened or confirmed by documentation of a positive family history and/or abnormal (increased) incubated osmotic fragility test, which is essentially a quantitative measure of spherocytes. Occasionally it is necessary to exclude other conditions in which spherocytes may be observed on the blood smear, such as Coombs positive autoimmune hemolytic anemia. Other abnormal test results include slight elevation in total and indirect bilirubin and decreased haptoglobin, features of any hemolytic anemia.

COMPLICATIONS

In addition to non-specific signs and symptoms of chronic hemolytic anemia, patients may have the following complications:

1. Aplastic Crisis: An aplastic crisis is due to an acute infection with parvovirus B19. This agent directly attacks erythroid precursors in the bone marrow and results in erythroid aplasia for approximately 10 days. Patients with a short red cell life span have a rapidly progressive anemia during this period of absent erythropoiesis. Patients typically present with marked pallor, lethargy, and fever. Sometimes there is a *decrease* in the degree of jaundice. The hemoglobin value is usually between 3 and 6 gm/dl. Reticulocyte count is typically less than 1%. A bone marrow examination or specific serologic tests for parvovirus are usually unnecessary. Management usually requires a packed red blood cell transfusion. These patients are contagious (via respiratory tract secretions), so contact isolation is required during hospitalization. Other family members with HS may also become infected (and should be checked). Following recovery from an aplastic crisis, permanent immunity usually results. Therefore, recurrent aplastic crises are extremely rare.
2. Hyperhemolytic Crisis: Far more common but less severe than aplastic episodes are hyperhemolytic crises characterized by acceleration of the usual hemolytic rate. These episodes usually accompany non-specific viral infections, in which the reticuloendothelial system undergoes hyperplasia, with further enlargement of the spleen. In contrast to an aplastic crisis, the hemoglobin is usually in the 5 to 8 gm/dl range (or even higher during more mild episodes), the reticulocyte count is elevated, and the patients are more jaundiced than usual. Blood transfusions are sometimes necessary. The episodes may be repetitive and prompt consideration of splenectomy (see below).
3. Gallstones: Any patients with chronic hemolytic anemia may develop bilirubin gallstones. The specific risk in HS is uncertain, but it may be as high as 50% by mid-adulthood. Gallstones are often asymptomatic, but they may cause problems, such as abdominal pain, fatty food intolerance, extreme jaundice due to obstruction of the common bile duct, and (rarely) biliary cirrhosis or carcinoma of the gallbladder.

4. Marrow expansion: Since red blood cells are made in the bone marrow, whenever there is increased production of red cells there is elevated “pressure” within the marrow, thus compressing and expanding the adjacent bone. This is especially prominent in the maxilla, the thinnest bone in the body. The expansion of this bone in children with HS and other hemolytic anemias may cause an overbite which requires orthodontic management.

MANAGEMENT

Most patients with HS are well and require no treatment. Supplemental iron, folic acid, or special diets are unnecessary. A complete blood count (the results of which are usually fairly constant in any given patient) need not be performed on a routine basis more than once or twice annually (except during the first year of life when more severe anemia may be present). Any time that a patient has a particularly severe infection or has marked pallor, increasing jaundice, or other evidence of an aplastic or hyperhemolytic crisis, an additional CBC and reticulocyte count should be performed. A packed red blood cell transfusion should be considered for symptomatic patients with symptomatic anemia. No restriction of activities is necessary, even in patients with palpable splenomegaly. Unlike conditions such as infectious mononucleosis where the spleen is acutely enlarged, there is no evidence that chronic splenomegaly predisposes to splenic rupture.

Splenectomy

The definitive treatment for HS is splenectomy. The hemolysis in HS is secondary to non-deformability of the spheroidal erythrocytes as they traverse the microcirculation of the spleen. In fact, the spleen is the primary organ in the body where these cells are destroyed. Therefore, splenectomy results in correction of the hemolytic anemia. Splenectomy is the preferred treatment for symptomatic patients with any combination of the following:

1. Moderate chronic anemia (hemoglobin less than 8 – 8.5 g/dl) with symptoms (malaise, decreased exercise tolerance, tiredness, etc), that interfere with the child’s quality of life.
2. Frequent hyperhemolytic episodes (more than once or twice each year) with a decline in hemoglobin to the symptomatic level or several such events requiring transfusion..
3. Marked splenomegaly, persistent jaundice, gallstones, growth retardation, or other findings consistent with severe hemolysis.

Splenectomy is almost always delayed until beyond 5 or 6 years of age, when the risk of post-splenectomy septicemia is somewhat less. However, a small risk of this fatal complication even in older children, teenagers, and adults. Therefore, the advantages of splenectomy (resolution of the anemia and of all of its complications, such as gallstones

and aplastic or hyperhemolytic crises) must be weighed against the risk of post-splenectomy septicemia. If splenectomy is performed, patients should be vaccinated several weeks preoperatively with conjugated pneumococcal vaccine (Pneumovax®) and (if they have not received it earlier) H. influenzae type b vaccine. Two months later they should receive a dose of 23-valent pneumococcal vaccine (Pneumovax). When possible, it is preferable to administer both Pnevmar and Pneumovax, two months apart, before splenectomy. Also consider giving the conjugated meningococcal vaccine. Twice daily prophylactic penicillin should be administered for at least 3 years following splenectomy, and the patient must be warned that for the remainder of their lives they should seek immediate medical attention for any high fever (101.5°F or above and/or shaking chills).

Febrile Illness

When evaluated with fever the asplenic patient should have a blood culture performed and receive an empiric dose of parenteral antibiotics (Rocephin or equivalent). Following splenectomy, it should be documented that the hemoglobin and reticulocyte counts have normalized (although microspherocytes will still be present on the blood smear). Afterwards the patient needs to be followed only once every year (primarily to provide reminders about the risk of septicemia and the need to take penicillin and seek medical attention for all febrile illnesses).

A second complication of splenectomy that is less well defined is thrombosis. There is emerging evidence that persons who have a splenectomy (either for hereditary spherocytosis or another condition) are predisposed to developing blood clots in their legs, lungs, heart, and brain. This is unproven and currently under study by us and other researchers.

Gallstones: Patients without abdominal pain or other symptoms of cholelithiasis do not require routine ultrasound examination (except prior to splenectomy). However, such investigations should be performed in symptomatic patients, and cholecystectomy should be performed if such symptoms (abdominal pain, episodes of marked jaundice, etc.) are severe or persistent. If splenectomy is going to be undertaken, preoperative abdominal ultrasound examination should be performed, so that if stones are present elective cholecystectomy can be performed at the time of the laparotomy or laparoscopic procedure. Whether patients with symptomatic gallstones as their only problem from the disease should have elective splenectomy performed at the same time is controversial and requires an individualized approach.

OUTCOME

Surprisingly little information is available about the long-term outcome of pediatric patients with HS who have been followed for decades, either with or without splenectomy. We assume that the majority of patients will do extremely well and live a normal life. With preventive vaccinations, prophylactic penicillin, and vigilance during times of febrile illnesses, deaths due to post-splenectomy septicemia are extremely rare.

Unfortunately, hereditary spherocytosis has been ignored by most medical researchers because there is a “cure” (splenectomy) and most “cured” patients are seemingly well. We greatly need more careful studies of persons with HS to better gauge the real impact of the condition on the person’s daily life. Having such evidence based data will allow us to make better evidence-based decisions about who should have splenectomy and who should be managed conservatively. Long-term follow-up of patients, whether they have had splenectomy or not, will be necessary in order to better assess the risks of septicemia and thrombosis and to determine, as has been suggested, whether leaving the spleen in actually protects persons with HS from thrombosis.

Anyone reading this brochure who has questions or concerns about hereditary spherocytosis should feel free to call me or a member of the hematology-oncology staff at the Children’s Medical Center Dallas and The University of Texas Southwestern Medical Center. Our telephone number is 214/456-2382 (days) or 214/456-7000 (nights and weekends). My e-mail address is: george.buchanan@utsouthwestern.edu.

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