Hereditary Spherocytosis

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Hereditary spherocytosis (HS) is a common inherited hemolytic anemia caused by abnormalities in spectrin, or in other proteins involved in the structural integrity and function of spectrin, such as ankyrin and protein 4.2, among others.

1. Pathophysiology:

   (a) These protein defects lead to a weakened osmotically fragile cell membrane in the patient's red blood cells (RBCs). "Conditioning" of RBCs occurs in the spleen where damaged RBCs are trapped and decreased oxygen and limited glucose availability contributes to their demise.
   (b) The deficiency leads to a remodeling of the usual biconcave disk into cells which resemble spheres. These abnormal cells have a shortened life span which contributes to anemia.
   (c) The spherical shape of patient RBCs results from a reduction in the amount of membrane material available thus producing a reduced surface to volume ratio and increase in cell density. As more membrane is lost, the limit of the RBC membrane stretching is reached and lysis occurs
   (d) Prevalence and inheritance:

      (i) Occurs in all racial groups but is most common in northern Europeans.
      (ii) 75 % of cases are of dominant inheritance and 25 % are recessive with new mutations common.
      (iii) Many mutations may cause phenotypic HS, with mutations often unique to each family

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C.P. Coppola et al. (eds.), *Pediatric Surgery*, DOI 10.1007/978-3-319-04340-1_52,
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2. Clinical Presentation

   (a) Patients present with varying degrees of anemia, jaundice (may wax and wane), increased reticulocyte count, variable splenomegaly, and often evidence of gall stones.
   (b) The CBC with differential shows spherocytes and a positive osmotic fragility test in conjunction with a family history is confirmatory. Patients red blood cell (RBC) indices are also helpful with the combination of elevated red blood cell distribution width (RDW) and increased mean corpuscular hemoglobin concentration (MCHC) are strongly suggestive of HS.
   (c) HS can be classified as mild, moderate and severe based on baseline hemoglobin, degree of reticulocytosis, and resting bilirubin levels. These clinical classifications correlate with degree of osmotic fragility (severe has more fragile RBCs) and spectrin content (mild having near normal spectrin, severe with less than 50 % of normal value).
   (d) In mild cases of HS there is a compensated hemolytic anemia with normal or near hemoglobin and mildly increased reticulocyte counts. These patients are asymptomatic at steady state and often only come to light during an illness (such as infectious mononucleosis), pregnancy or physical stress (military training).
   (e) Severely affected patients have significant anemia and are transfusion dependent. Peripheral smears in these patients show spherocytes as well as bizarrely shaped cells (poikilocytes). Growth failure, and delayed sexual maturation are common and these patients are at risk for severe aplastic crises (later).
   (f) Moderately affected patients usually do well but may become symptomatic when stressed (i.e. illness, significant physical exertion).
   (g) Neonates with HS often have prolonged jaundice. Anemia during the first year of life may necessitate transfusions. There may be a role for erythropoietin in these infants. The osmotic fragility test, if done during the newborn period, should have newborn cells as controls.

3. Diagnosis:

   (a) Laboratory evaluation:

      (i) Hereditary spherocytosis is a hemolytic anemia and thus laboratory values are consistent with this and include: reticulocytosis, indirect hyperbilirubinemia, and variable anemia. The hemolysis is mainly extravascular and thus haptoglobin and lactate dehydrogenase (LDH) are poor indicators of hemolysis. The peripheral smear is diagnostic and shows spherocytes with RBC indices remarkable for an elevated RDW and MCHC. Other important causes of spherocytic anemias such as autoimmune hemolytic anemia can be distinguished by the negative coombs test in HS.
      (ii) Osmotic fragility (OF) testing: this test is performed by exposing control and suspected HS cells to increasingly hypotonic sodium chloride concentrations. Normal cells are able to swell and increase their volume

since they are starting as a normal biconcave disc. HS cells already have a decreased surface to volume ratio (spheres) and thus reach their limit at a higher concentration of sodium chloride compared to normal cells. The incubated OF test is the gold standard and consists of a period of incubation (24 h at 37 °C) prior to exposure to the saline concentrations which metabolically depletes the cells and making the test more sensitive.

(b) Differential diagnosis:

(i) Blood group ABO incompatibility and other immunohemolytic anemias: morphology of the RBCs is similar but HS lacks a positive coombs test. It is important to include a C3 Coombs test (as a test for a positive IgM antibody) in the evaluation of a suspected immune mediated hemolytic anemia if the IgG Coombs test is negative.
(ii) Heinz body anemias: spherocytes may be seen but are usually not the predominant cell. Rather, so called bite or blister cells are more common.
(iii) Undiagnosed patients presenting in aplastic crises- this may be confusing since the reticulocyte count will be low and the bilirubin level may also be falsely low.

4. Treatment:

(a) Routine care:

(i) Patients should be followed by a hematologist or a pediatrician familiar with this disease and its complications.
(ii) Baseline (several) hemoglobin levels, bilirubin levels and reticulocyte counts are helpful to document a significant change in the event of illness.
(iii) Counseling concerning the various crises must be discussed, especially aplastic crisis with parvovirus B19 (this particular variety of crises is not obvious and signs and symptoms must be understood by caretakers).
(iv) Counseling concerning indications, risks, and benefits of splenectomy must be discussed and understood in patients who are candidates for this procedure.
(v) Palpation of the spleen and avoidance of contact sports during periods of significant enlargement must be taught to families. The use of abdominal padding/protection is an option in patients who strongly desire to participate in contact sports.
(vi) Folic acid should be prescribed and reasons for its use understood.
(vii) Patients who have undergone splenectomy must be educated and reminded of the risks for sepsis and thrombosis. Penicillin prophylaxis is indicated immediately following splenectomy but the length of administration is under debate. Immunizations should be administered.
(viii) Signs and symptoms of gallstones and gallbladder disease should be discussed as well as indications for cholecystectomy.

(b) Splenectomy

(i) Splenectomy ameliorates the anemia, hyperbilirubinemia and reticulocytosis of most patients with HS. Spherocytes and a positive osmotic testing result are still present. The risk of post splenectomy sepsis must be considered and if splenectomy is to be done it should not occur till after age 5-years-old.

(ii) Postsplenectomy sepsis is a serious complication and may be fatal. Streptococcus pneumonia, Neisseria meningitidis and Haemophilus influenza type b are the major organisms and vaccination should be done before splenectomy occurs. It is unclear if the risk of overwhelming sepsis lessens over time.

(iii) Thrombosis and thromboembolism: the overall risk after splenectomy is between 1.5 and 55 %. Portal vein thrombosis incidence after splenectomy is believed to be between 6.3 and 10 % while that of stroke or ischemic heart disease is increased in HS patients who underwent splenectomy as compared to HS patients who did not.

(iv) The cause of this is not well understood but may relate to thrombocytosis which occurs after splenectomy, the presence of an increased number of abnormal RBCs in circulation triggering platelet aggregation, and release of free hemoglobin into the vasculature leading to decreased nitric oxide.

(v) Further studies are needed to understand this significant post splenectomy complication.

(vi) Indications for splenectomy:

1. Indications for splenectomy must be clear and the cost benefit ratio must be understood by all involved in the decision making.
2. Patients with severe disease who are transfusion dependent and showing growth disturbances should undergo splenectomy.
3. Other compelling but not absolute indications include physical limitations due to anemia, leg ulcers, or when extramedullary hematopoiesis is significant.

(vii) A laparoscopic approach is the method of choice and partial splenectomy is an increasingly considered and used option, especially in light of the increased risk for thrombosis and sepsis after total splenectomy.

(viii) Partial splenectomy: near total splenectomy by removing all splenic pedicles except the left gastroepiploic vessel.

(ix) Embolization has also been used: regrowth of the spleen with increased hemolysis may occur.

5. Complications:

(a) Gallstones: the presence of bilirubin containing gallstones is common. Ultrasound is a non-invasive method for diagnosis and should be done every 5 years to access the presence of stones. If stones are detected cholecystectomy is indicated for recurrent symptoms or obstruction.

(b) Increased hemolysis: these may occur in the setting of acute infection and are marked by increasing bilirubinemia, enlargement of the spleen, anemia and increased reticulocytosis. Management is conservative and transfusions may be indicated.
(c) Aplastic crises: these occur as a result of viral infections including parvovirus B19 (fifth disease) and are marked by anemia (may be severe) and reticulocytopenia. Symptoms may be severe and transfusions may be necessary to treat/prevent congestive heart failure. The etiology of this complication lies in the shortened life span of RBCs in patients with HS. Cessation of RBC production for 10 days in patients with normal RBC lifespan (120) days results in an 8–10 % drop in hemoglobin. RBCs from HS patients may have a life span of 20 days resulting in a 50 % reduction in hemoglobin often starting from a lower baseline hemoglobin level.
(d) Megaloblastic crises: these may occur during periods of time of increased RBC production which outstrips the body's supply of folate (such as pregnancy). These may be easily prevented by the administration of folic acid.

Suggested Further Reading

Grace RF, Lux SE, Chapter 15: Disorders of the Red Cell Membrane. Nathan and Oski's hematology of infancy and childhood, 7e, Saunders, Philadelphia, 2009; p. 714–45.
Tracy E, Rice H. Partial splenectomy for hereditary spherocytosis. Pediatr Clin North Am. 2008;55(2):503–19.