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## REVIEW ON: HEREDITARY SPHEROCYTOSIS

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**Abstract:** Hereditary spherocytosis is a common and very common anemia of hemolytic anemia caused by a deficiency of red cell membrane proteins. In recent years, major advances in our understanding of red cell membranes and the better structure of its components have allowed a clearer understanding of the pathogenesis of this disease. In this article, we present an overview of the erythrocyte bone and its unique components. we also review the clinical features of the disease and describe current cell defects involving membrane proteins that have been shown to play an important role in the inherited spherocytosis. Current diagnostic tests for hereditary spherocytosis (HS) focus on the detection of hemolysis or indirectly assessing defects of membrane protein, whereas direct methods to detect protein defects are complicated and difficult to implement.

**Keywords:** Hereditary spherocytosis, a plastic crisis, anemia, hemolysis

### Introduction:

**Hereditary spherocytosis** is an abnormality of red blood cells, or erythrocytes. The disorder is caused by mutations in genes relating to membrane proteins that allow for the erythrocytes to change shape.<sup>1, 2</sup> The abnormal erythrocytes are sphere-shaped (spherocytosis) rather than the normal biconcave disk shaped. Dysfunctional membrane proteins interfere with the cell's ability to be flexible to travel from the arteries to the smaller capillaries<sup>3, 5</sup>. this difference in shape also makes the red blood cells more prone to rupture. Cells with these dysfunctional proteins are degraded in the spleen. This shortage of erythrocytes results in hemolytic anemia. It is the most common cause of inherited hemolysis in European and North American Caucasian populations, with an incidence of 1 in 5000 births. The clinical severity of HS varies from symptom-free carrier to severe hemolysis because the disorder exhibits incomplete penetrance in its expression. Symptoms include anemia, jaundice, splenomegaly, and fatigue. Furthermore, the detritus of the broken-down blood cells

– unconjugated or indirect bilirubin – accumulates in the gallbladder, and can cause pigmented gallstones to develop. In chronic patients, an infection or other illness can cause an increase in the destruction of red blood cells, resulting in the appearance of acute symptoms, a *hemolytic crisis*. On a blood smear, Howell-Jolly bodies may be seen within red blood cells. Primary treatment for patients with symptomatic HS has been total splenectomy, which eliminates the hemolytic process, allowing normal hemoglobin, reticulocyte and bilirubin levels. Acute cases can threaten to cause hypoxia through anemia and acute kernicterus through high blood levels of bilirubin, particularly in newborns. Most cases can be detected soon after birth. An adult with this disease should have their children tested, although the presence of the disease in children is usually noticed soon after birth. Occasionally, the disease will go unnoticed until the child is about 4 or 5 years of age<sup>4,6</sup>. A person may also be a carrier of the disease and show no signs or symptoms of the disease. Other symptoms may include abdominal pain that could lead to the removal of the spleen and/or gallbladder. Spherocytosis patients who are heterozygous for a hemochromatosis gene may suffer from iron overload, despite the hemochromatosis genes being recessive.

## COMPLICATIONS

- Hemolytic crisis, with more pronounced jaundice due to accelerated hemolysis (may be precipitated by infection).
- Aplastic crisis with dramatic fall in hemoglobin level and (reticulocyte count)-decompensation, usually due to maturation arrest and often associated with megaloblastic changes; may be precipitated by infection, such as influenza, notably with parvovirus B19.
- Folate deficiency caused by increased bone marrow requirement.
- Pigmented gallstones occur in approximately half of untreated patients. Increased hemolysis of red blood cells leads to increased bilirubin levels, because bilirubin is a breakdown product of heme. The high levels of bilirubin must be excreted into the bile by the liver, which may cause the formation of a pigmented gallstone, which is composed of calcium bilirubinate. Since these stones contain high levels of calcium carbonates and phosphate, they are radiopaque and are visible on x-ray.
- Leg ulcer.
- Abnormally low hemoglobin A1C levels.[8] Hemoglobin A1C (glycated hemoglobin) is a test for determining the average blood glucose levels over an extended period of time, and is often used to evaluate glucose control in diabetics. The hemoglobin A1C levels are abnormally low because the life span of the red blood cells is decreased, providing less time for the non-enzymatic glycosylation of hemoglobin. Thus, even with high overall blood sugar, the A1C will be lower than expected.<sup>7</sup>

## **PATHOPHYSIOLOGY**

Hereditary spherocytosis can be an autosomal recessive or autosomal dominant trait. Hereditary spherocytosis is most commonly (though not exclusively) found in Northern European and Japanese families, although an estimated 25% of cases are due to spontaneous mutations. A patient has a 50% chance of passing the mutation onto each of his/her offspring.

Hereditary spherocytosis is caused by a variety of molecular defects in the genes that code for the red blood cell proteins spectrin (alpha and beta), ankyrin, band 3 protein, protein 4.2, and other red blood cell membrane proteins.<sup>7,8</sup>

These proteins are necessary to maintain the normal shape of a red blood cell, which is a biconcave disk. The integrating protein that is most commonly defective is spectrin which is responsible for incorporation and binding of spectrin, thus in its dysfunction cytoskeletal instabilities ensue.<sup>5,6,9</sup>

The primary defect in hereditary spherocytosis is a deficiency of membrane surface area. Decreased surface area may be produced by two different mechanisms: 1) Defects of spectrin, ankyrin (most commonly), or protein 4.2 lead to reduced density of the membrane skeleton, destabilizing the overlying lipid bilayer and releasing band 3-containing microvesicles. 2) Defects of band 3 lead to band 3 deficiency and loss of its lipid-stabilizing effect. This results in the loss of band 3-free microvesicles. Both pathways result in membrane loss, decreased surface area, and formation of spherocytes with decreased deformability.<sup>10</sup>

As the spleen normally targets abnormally shaped red cells (which are typically older), it also destroys spherocytes. In the spleen, the passage from the cords of Billroth into the sinusoids may be seen as a bottleneck, where red blood cells need to be flexible in order to pass through. In hereditary spherocytosis, red blood cells fail to pass through and get phagocytosed, causing extravascular hemolysis.<sup>11</sup>

## **DIAGNOSIS**

In a peripheral blood smear, the red blood cells will *appear* abnormally small and lack the central pale area that is present in normal red blood cells. These changes are also seen in non-hereditary spherocytosis, but they are typically more pronounced in hereditary spherocytosis. The number of immature red blood cells (reticulocyte count) will be elevated. An increase in the mean corpuscular hemoglobin concentration is also consistent with hereditary spherocytosis.<sup>12</sup>

Other protein deficiencies cause hereditary elliptocytosis, pyropoikilocytosis or stomatocytosis. In longstanding cases and in patients who have taken iron supplementation or received numerous blood transfusions, iron overload may be a significant problem. This is a potential cause of heart muscle damage and

liver disease. Measuring iron stores is therefore considered part of the diagnostic approach to hereditary spherocytosis.

An **osmotic fragility test** can aid in the diagnosis. In this test, the spherocytes will rupture in liquid solutions less concentrated than the inside of the red blood cell. This is due to increased permeability of the spherocyte membrane to salt and water, which enters the concentrated inner environment of the RBC and leads to its rupture. Although the osmotic fragility test is widely considered the gold standard for diagnosing hereditary spherocytosis, it misses as many as 25% of cases. Flow cytometric analysis of eosin-5'-maleimide-labeled intact red blood cells and the **acidified glycerol lysis test** are two additional options to aid diagnosis.<sup>10,13</sup>

## TREATMENT

Although research is ongoing, at this point there is no cure for the genetic defect that causes hereditary spherocytosis. Current management focuses on interventions that limit the severity of the disease. Treatment options include:<sup>14</sup>

**Splenectomy:** As in non-hereditary spherocytosis, acute symptoms of anemia and hyperbilirubinemia indicate treatment with blood transfusions or exchanges and chronic symptoms of anemia and an enlarged spleen indicate dietary supplementation of folic acid and splenectomy, the surgical removal of the spleen. Splenectomy is indicated for moderate to severe cases, but not mild cases. To decrease the risk of sepsis, post-splenectomy spherocytosis patients require immunization against the influenza virus, encapsulated bacteria such as *Streptococcus pneumoniae* and meningococcus, and prophylactic antibiotic treatment. However, the use of prophylactic antibiotics, such as penicillin, remains controversial.<sup>15</sup>

**Partial splenectomy:** Since the spleen is important for protecting against encapsulated organisms, sepsis caused by encapsulated organisms is a possible complication of splenectomy. The option of partial splenectomy may be considered in the interest of preserving immune function. Research on outcomes is currently limited, but favorable. Surgical removal of the gallbladder may be necessary.<sup>15, 16</sup>

## Conclusions:

Undiagnosed hereditary spherocytosis may lead to inpatient transfusions for severe anemia. Earlier detection of hereditary spherocytosis is easily achievable and may reduce hospitalizations via closer monitoring.

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