Hereditary Spherocytosis Disease

Hereditary spherocytosis is a predominantly autosomal dominant disease due to a defect in proteins (spectrin or ankyrin) that comprise the RBC membrane. This forms less flexible, spheroid RBCs that are more susceptible to splenic destruction, and results in a hemolytic anemia that is characterized by bilirubin gallstones, jaundice, and splenomegaly.



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Northern Europeans
North-compass European
Hereditary spherocytosis (HS) affects Northern Europeans at the highest rate, with reports indicating occurrences in these populations at 1 in 5000.

Mechanisms

Autosomal Dominant
Domino
Up to 3/4 of cases are autosomal dominant, while the remaining cases occur in an autosomal recessive pattern.

Spectrin/Ankyrin Deficiency
Spackle/Anchor-ring
Two deficient RBC membrane proteins, called spectrin and ankyrin, are primarily responsible for causing hereditary spherocytosis (HS). Ordinarily, ankyrin acts as the binding site for spectrin on RBC membranes. Spectrin then operates as a structural protein that maintains the biconcave shape, flexibility and membrane stability of healthy RBCs. However, in the most common pathogenesis of HS, a mutated ankyrin gene results in insufficient ankyrin on RBC membranes, depriving spectrin of a binding site which results in the membrane instability and structural defect of spherical RBCs, or spherocytes. This disease can also occur from defects in protein 4.2, which is a RBC cytoskeletal protein, or in band 3, which physically links the plasma membrane to the underlying membrane skeleton.

Spherocyte Formation
Sphere-cell Forming
Reduced RBC membrane stability results in the formation of spherocytes, or spherical RBCs. This shape shifting transformation from biconcave to spherical places these defective RBCs at risk for destruction as they attempt to traverse the turbulent, confined spaces of microcirculation, particularly in the spleen, where shearing forces can result in fragmented RBCs called schistocytes, among other hemolytic by-products. These cells lack the central pallor of normal RBCs. They are also seen in autoimmune hemolytic anemia.

Hemolytic Anemia
Hemolysing-RBCs from Anemone
Spherocytes have difficulty passing through microcirculation due to their reduced flexibility. They have the greatest trouble passing through the spleen where they become obstructed, fragmented (schistocytes) and otherwise destroyed by phagocytosis via macrophages, resulting in a hemolytic anemia. Spherocytes last only 10-20 days vs. the 120 day life cycle of normal RBCs.

Symptoms

Bilirubin Gallstones
Belly-ribbon-dancer and Gold-stones
In this disorder, RBC destruction results in excess bilirubin and subsequently places patients at risk for bilirubin gallstone formation. As such, cholelithiasis is a common manifestation of hereditary spherocytosis in affected adults.

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Jaundice

Jaundice-janitor

Jaundice, or yellowing of the skin secondary to excess bilirubin, results from the catabolism of heme to bilirubin that occurs from hemolytic anemia.

Splenomegaly

Spleen-balloon

Hypersplenism, which describes a hyperactive spleen, occurs because of the increased functional burden of phagocytosing spherocytes that occurs in the spleen, resulting in splenic enlargement. This is seen in hereditary spherocytosis, along with all other extravascular hemolytic anemias.

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