Definition

Hereditary spherocytosis (HS) is a relatively common and highly variable inherited disorder of the red blood cells. In HS, red blood cells become sphere−shaped, instead of the usual biconcave (hourglass) shape. The hourglass shape is vital for the blood cells to function−−it offers increased surface area so that oxygen and carbon dioxide can diffuse more easily through the cell's tissue, and the shape lets the cells circulate more easily in tight places, like small capillaries. These *spherocytes* are broken down more quickly than normal red blood cells, resulting in anemia and related complications.

Description

Hereditary spherocytosis results from a molecular change in one of the proteins making up the cytoskeleton of the red blood cell. The cytoskeleton consists of the network of proteins that support and maintain the integrity of the red cell membrane. Genetic mutations in membrane proteins lead to loss of these and related membrane components. As the membrane becomes unstable and the surface area of the membrane decreases, spherocytes form. The spleen provides an environment that encourages spherocyte formation. Due to their increased rigidity, spherocytes tend to become trapped in the spleen and then broken down by macrophages, specialized white blood cells. This hemolytic process most often leads to mild, chronic anemia. Depending in part on the particular genetic mutation underlying HS in a given individual, anemia can also be severe and require chronic blood transfusions. Additional complications related to anemia can arise.

Demographics

HS has been seen in individuals of many ethnic backgrounds, but is particularly common among people of northern European background, affecting about one in 5,000 of such individuals.

Genetic profile

About 75% of all cases of HS are due to the presence of an autosomal dominant mutation, one in which the mutated gene is passed on from either parent. Most of these cases result from the inheritance of a mutation from one parent, but a fourth of these cases are sporadic and due to a new mutation that has occurred in the affected individual. A minority of cases of HS is recessively inherited. HS−causing mutations have been described in four genes, each of which codes for a protein involved in maintaining stability of the red blood cell membrane. The cytoskeleton can be thought of as a "scaffolding" or "frame" that is attached to and maintains the "wall" that is the cell membrane. The red cell membrane is made up of lipids, which are fat and fat−like molecules, and proteins called integral membrane proteins. The cytoskeleton lies just below the cell membrane and is made up of additional proteins, including spectrin, ankyrin, protein 4.1, and others.

Ankyrin

The ankyrin gene is located on the short arm of chromosome 8 (8p11.2). As of 1998, a total of 34 mutations in the ankyrin gene have been associated with HS. These account for 35−65% of all HS cases, including both dominant and recessive forms. Dominant−acting mutations tend to be those that result in a shortened ankyrin protein, including so−called frameshift and nonsense mutations. Recessive−acting mutations tend to be those that result in subtler changes to the protein. These include so−called missense mutations that result in the substitution of a single amino acid−−the building block of proteins−−which can have an effect on protein function. Recessive mutations also include those in the area "upstream" from the gene, in the promoter region that helps determine the quantity of protein made from the gene. Rarely, spherocytosis can be one symptom within a larger syndrome that is due to a deletion of a portion of chromosome 8. Such a microdeletion syndrome can affect several genes including the ankyrin gene, and there can be a range of physical and mental effects.

Spectrin

Spectrin is a cytoskeleton protein made of two components: alpha spectrin and beta spectrin. Two recessive mutations have been identified in the alpha spectrin gene on chromosome 1. This recessive form of the disease tends to have relatively severe hemolytic anemia. As of 1998, 19 mutations have been described in the beta spectrin gene on chromosome 14. These result in dominantly inherited HS.

Band 3 and others

Mutations in the gene for band 3, an integral membrane protein, account for 15−25% of all cases of HS. Five dominant mutations have been described, most of which result in a shortened protein. Disease−causing mutations in other cytoskeleton or red cell membrane proteins are rare but have been described.

Modifying genetic factors

Disease severity is not only affected by the nature of the primary genetic mutation; it is also impacted by other genetic variations. Individuals with HS who also have Gilbert syndrome have an increased risk of gallstones. Gilbert syndrome is caused by a change in the UGT 1A1 gene that results in increased levels of bilirubin. Researchers have also hypothesized that persons with other inherited or acquired forms of hemolytic anemia may also be at increased risk of gallstones if they also have a disease−causing HS mutation. The presence of hereditary hemochromatosis in addition to HS increases the propensity toward iron−overload. Hereditary hemochromatosis is a relatively common recessive condition that can lead to organ failure due to iron−overload, if untreated.

Signs and symptoms

Symptoms of HS can be extremely variable. Some individuals may experience onset as early as the neonatal period and require treatment. Others may have only mild anemia that does not require treatment and does not become evident until later in life. Some individuals with few and subtle signs may even go undiagnosed. Variability is largely influenced by the primary underlying genetic mutation, with the recessive forms of the disease tending to be most severe. This does not account for all the variability, however, given that multiple affected individuals within the same family carrying the same genetic mutation may have symptoms of varying severity. The effects of modifying genes or environmental factors may contribute to this additional variability.

Anemia

The red blood cell membrane has increased fragility in HS. Therefore, red cells are more easily broken down, a symptom called hemolytic anemia. This occurs primarily in the spleen. The spleen filters out old and abnormal red blood cells, as well as fights infection from bacteria, particularly the encapsulated type. Anemia can be unnoticeable or mild, or it can be rapid and severe. Rapid, acute breakdown of red blood cells can occur as a result of exposure to chemicals or medications that are known to further increase red cell membrane fragility. It can also occur as a result of infection that increases the hemolytic activity of the spleen or decreases red blood cell production. Acute aplastic anemia events, in which red blood cell production halts, can occur with deficient folate levels or following infection by a specific virus called parvovirus.

Jaundice

Jaundice occurs when the level of bilirubin, a breakdown product of hemoglobin, increases. As red blood cells breakdown rapidly, the liver may not be able to keep up with the increased need to metabolize bilirubin, which can deposit in the skin and eyes causing a yellowish discoloration.

Gallstones

Bilirubin levels can also be increased in the bile. Bile is the fluid secreted by the liver into the intestine. Bile reaches the intestine by passing through the gallbladder and bile duct. Excess bilirubin can form stones in the gallbladder early in life.

Hemochromatosis

Hemochromatosis, or high iron levels, is also characteristic of HS. Iron−overload can lead to dysfunction of organ systems, including the endocrine system, which directs hormone levels.

Other complications

Leg ulcers are also seen in HS, and acute kidney failure due to hemolytic anemia is a rare complication. Rarely, HS can be seen within a syndrome as one symptom in combination with other complications such as neurological problems and other congenital physical differences. Such syndromes may be caused by the deletion of a portion of a chromosome including a gene known to be associated with HS, among other genes.

Diagnosis

HS must be distinguished from other causes of hemolytic anemia that can resemble HS. These include immune hemolytic anemia, G6PD deficiency, unstable hemoglobin traits or diseases, Wilson disease, and spherocytosis due to burn injury or toxin exposure (i.e. clostridia−−bee, spider, or snake venom). Routine blood tests are typically sufficient to diagnose HS, particularly if an individual is showing symptoms. A peripheral blood smear, which is a slide preparation of a blood sample, will show the presence of a number of spherocytes that are uniform in appearance. Bilirubin levels tend to be elevated. A complete blood count will show several abnormalities. Hemoglobin levels tend to be decreased. Reticulocytes, which are immature red blood cells, tend to be increased. Red blood cells tend to be smaller than normal, which is marked by a decreased mean cell volume (MCV). The mean cell hemoglobin concentration (MCHC) tends to be high, which is a reflection of the overall decrease in the cell volume. Ektacytometry is a specialized test that can demonstrate the fragility of the red blood cell membrane by placing the cells under stress and identifying increased levels and specific patterns of hemolysis. Another specialized test called the rapid flow cytometric test has recently been developed. This test can determine differences in fluorescent staining patterns that distinguish normal red blood cells from those that are characteristic of HS. This test is highly sensitive and specific for HS and should aid in its rapid diagnosis.

Treatment and management

Most individuals with HS do not have symptoms that are severe enough to require treatment. For those with the more severe forms, blood transfusion therapy can effectively improve symptoms until a child is old enough for total or partial removal of the spleen, the organ responsible for most of the red blood cell destruction. Splenectomy most often eliminates HS complications. However, there is some risk remaining for ongoing chronic anemia or acute anemic events, particularly those caused by viruses and other factors that can temporarily halt red blood cell production. Splenectomy can also lead to an increased risk for blood clots, as well as life−threatening bacterial infection given the spleen's role in fighting bacterial infections. Studies have shown that partial, as opposed to total, splenectomy can be effective at ameliorating HS symptoms while also maintaining the bacterial−fighting capacity of the spleen and decreasing the chance for blood clots. Prophylactic antibiotics (i.e. penicillin) and additional vaccinations for common bacterial infections also play a role in decreasing negative side−effects of partial or total splenectomy. Surgery may be needed to remove gallstones that become symptomatic, which usually does not occur until after age 10 years.

Prognosis

Prognosis is very good for all types of HS, particularly the more mild forms. Treatment is very effective for the more severe forms. There is only a small number of affected individuals who still experience anemia and other symptoms following splenectomy.

Resources

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