AUTOIMMUNE HEMOLYTIC ANEMIA

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This article describes the symptoms, causes, diagnosis, disease course, and treatment of idiopathic or autoimmune hemolytic anemia (AIHA).

Anemia

Anemia is a blood disorder characterized by deficient red blood cells (RBCs). Anemia can be caused by congenital disorders; blood loss; nutrient deficiencies; inadequate RBC production; and increased destruction or lysis of RBCs. In lysis or hemolysis, the term used for lysis of RBCs, the cell's outer membrane is ruptured. Hemolysis releases hemoglobin, the blood protein that carries oxygen to tissues, from RBCs, destroying them. Normally, RBCs survive for about 120 days and then begin to disintegrate. New RBCs are constantly produced in the bone marrow and replace the old, disintegrating cells. This cell lifespan or programmed cell death is known as apoptosis.

Hemolytic Anemia

Anemias associated with hemolysis are known as hemolytic anemias. In hemolytic anemia, normal apoptosis is altered, and RBCs are destroyed faster than the body can replace them. When an autoimmune process causes hemolytic anemia, the resulting disorder is called autoimmune hemolytic anemia or AIHA.

AIHA

In AIHA the immune system mistakenly identifies RBCs as foreign substances. Consequently, the immune system produces autoantibodies that attack and destroy RBCs. Women are affected about twice as often as men, and people of any age can be affected although AIHA generally occurs before age 50.

AIHA can occur in association with other autoimmune disorders, such as systemic lupus erythematosus (SLE) or it can be caused by the use of certain medications. In about half of all cases, the specific cause of AIHA can't be determined. These conditions are called idiopathic AIHA. AIHA may occur suddenly, causing acute anemia or it can develop gradually. In some cases AIHA resolves after several months to years, although it can persist indefinitely, causing chronic anemia.

AIHA is also known as immune hemolytic anemia, acquired hemolytic anemia, immune mediated anemia, and idiopathic autoimmune hemolytic anemia. When AIHA occurs as the only disorder it is known as primary AIHA. When AIHA develops in patients who have another associated medical condition, it's called secondary AIHA.

Cold and Warm Subtypes of AIHA
Two basic subtypes of AIHA have been identified: 1) warm antibody hemolytic anemia and 2) cold antibody hemolytic anemia. Here, warm and cold refer to the temperature at which the autoimmune cell destruction occurs. Warm antibodies cause 80-90 percent of AIHA, and cold antibodies cause the remaining cases.

In warm AIHA, which is primarily idiopathic, autoantibodies are composed of immunoglobulin G (IgG), they bind RBCs at 37°C (normal body temperature), and they alter RBCs, changing them into spherocytes. Identified causes of warm AIHA include non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), SLE, myeloma, human immunodeficiency virus (HIV) infection, hepatitis, collagen vascular diseases, and numerous medications, including methyldopa, quinidine, acetaminophen, ibuprofen, interferon alfa, hydrochlorothiazine, sulfa compounds, insulin, cephalothin, hydralazine, streptomycin, rifampin, and penicillin. When AIHA occurs as a secondary disorder associated with another medical condition, treatment of the other condition can improve AIHA. When AIHA occurs together with autoimmune thrombocytopenic purpura, an autoimmune disorder causing low platelet counts, it's known as Evans' syndrome. Evans syndrome has been reported to occur in patients with myasthenia gravis and other autoimmune conditions.

In warm AIHA, when warm autoantibodies attach to the RBC surface, they're recognized as foreign and ingested by white blood cells known as macrophages present in the spleen. This causes the RBCs to appear as spherocytes, which are inflexible compared to normal RBCs. Spherocytes become easily trapped in the spleen and removed from the blood circulation. The spleen normally filters and removes old and destroyed RBCs.

Cold antibody AIHA is caused by autoantibodies of the immunoglobulin M (IgM) subclass or by complement, an immune system chemical. In cold AIHA, IgM antibodies bind to RBC membranes at 32°C. Causes of cold AIHA include: infection with microorganisms, particularly HIV and Mycoplasma pneumonia; infectious mononucleosis, and lymphoma. Cold AIHA may also be idiopathic. Paroxysmal cold hemoglobinuria (condition of transient blood in urine) or PCH is a subtype of cold AIHA associated with tertiary syphilis and acute viral infections, including mumps and measles.

**Symptoms**

Symptoms in AIHA vary according to the severity of the condition. Common symptoms include fever, fatigue, pale skin, weakness, dizziness, confusion, low blood pressure, intolerance to physical activity, enlarged liver, increased heart rate and heart murmur. When RBC destruction is rapid, mild jaundice, a yellowing of the skin and eyes associated with dark urine can occur. If RBC destruction persists for extended periods, the spleen can become enlarged, causing symptoms of abdominal fullness or bloating.

**Diagnosis**
The blood count in AIHA shows decreased RBC, hemoglobin and hematocrit (percent of red blood cells to total blood volume). The RBCs are large, which is increased by an elevated mean corpuscular volume (MCV) and spherocytes are often noted. Increased RBC production, caused by increased RBC destruction, causes an increase in new RBCs or reticulocytes, resulting in an increased reticulocyte count. In addition, the enzyme lactic dehydrogenase (LDH) is usually elevated and levels of the protein haptoglobin are low. Autoantibodies that have latched onto RBCs are identified by a positive direct Coombs test, and antibodies freely circulating in blood are identified by an indirect Coombs test. In patients with jaundice, the indirect bilirubin level is also elevated.

**Treatment**

When symptoms are mild and RBC destruction slight, no treatment is required. If RBC destruction is worsening, corticosteroids such as prednisone are used. Initially, high doses of corticosteroids are used, followed by a gradual tapering of the dose over weeks or months. In patients who don't respond to steroids, other immunosuppressive agents such as cyclophosphamide are sometimes used. Alternately, surgery to remove the spleen (splenectomy) may be performed or a procedure known as plasmapheresis may be used. In plasmapheresis, blood is removed and filtered to remove antibodies, and then replaced. If the hemoglobin count falls to critical levels, blood transfusions are indicated although they provide temporary relief without offering a cure.

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