CONDITION

Cold agglutinin disease

Learn how cold agglutinin disease causes red blood cell breakdown, which symptoms may occur, and how the condition is diagnosed, treated, and monitored.

WHAT IT IS
Rare autoimmune blood disorder

BODY SYSTEM
Blood and immune system

MAIN SYMPTOMS
Fatigue, shortness of breath, jaundice, dark urine

WHAT CAUSES IT
Abnormal immune antibody

HOW IT IS DIAGNOSED
Hemolysis tests, direct antiglobulin test, cold agglutinin titer

MAIN TREATMENT
Complement inhibition or B-cell-directed therapy

CAN IT BE CURED?
No, treatments reduce hemolysis, not cure

IS IT AN EMERGENCY?
Sometimes, chest pain or severe difficulty breathing

LONG-TERM OUTLOOK
Variable from mild stable anemia to severe hemolysis

Overview

Cold agglutinin disease, or CAD, is a rare autoimmune blood disorder. It causes the immune system to attack red blood cells, especially when blood is exposed to cooler temperatures.

In CAD, an abnormal antibody-usually a type called immunoglobulin M, or IgM-attaches to red blood cells. These antibodies are called cold agglutinins because they can make red blood cells clump together in cooler parts of the body, such as the fingers, toes, ears, and nose.

The attached antibody also activates complement, a group of immune proteins in the blood. Complement marks red blood cells for removal, mainly by the liver. This process is called hemolysis. If red blood cells are destroyed faster than the bone marrow can replace them, hemolytic anemia develops.

CAD is different from having cold hands or being unusually sensitive to winter weather. It is also different from cold agglutinin syndrome, which is a similar pattern of hemolysis caused by another condition, such as an infection or certain cancers.

The severity of CAD varies. Some people have mild, stable anemia, while others have ongoing fatigue, circulation symptoms, or episodes of more severe hemolysis. Infections and cold exposure can make symptoms worse.

Symptoms

Symptoms may come from anemia, red blood cell breakdown, or clumping of red blood cells in small blood vessels.

Symptoms related to anemia may include:

Hemolysis may cause yellowing of the skin or whites of the eyes, called jaundice. Urine may appear dark because red blood cell contents are being cleared from the body.

Cold-induced circulation symptoms often affect the fingers, toes, ears, nose, or other exposed areas. The skin may become bluish or purple, which is called acrocyanosis. Some people have numbness, discomfort, or color changes similar to Raynaud phenomenon.

Symptoms do not always match the outdoor temperature. Cool indoor rooms, air conditioning, refrigerated food areas, cold drinks, or cold medical fluids may also trigger problems. A fever or infection can increase hemolysis even without major cold exposure.

- Fatigue, weakness, or reduced ability to exercise
- Shortness of breath, especially during activity
- Dizziness, headaches, or difficulty concentrating
- A rapid heartbeat or awareness of the heartbeat
- Pale skin

Causes and risk factors

CAD develops when a small group of abnormal B cells in the bone marrow produces cold-reacting antibodies. B cells are immune cells that normally make antibodies to fight infection. In CAD, the antibody is usually a monoclonal IgM antibody, meaning it comes from one group of similar B cells.

The antibody binds most strongly at low temperatures. However, the temperature range at

which it remains active-called its thermal amplitude-is often more important than the exact antibody level. An antibody that reacts at temperatures closer to normal body temperature is more likely to cause clinically important hemolysis.

CAD is considered a distinct bone marrow B-cell disorder. Many people have a small abnormal B-cell population without having an aggressive lymphoma. A hematologist may still evaluate the bone marrow and blood for an underlying lymphoid cancer because the distinction affects diagnosis and treatment.

Cold agglutinin syndrome is secondary to another illness rather than being a primary disorder. Possible causes include certain infections, autoimmune diseases, and lymphomas. Infections associated with temporary cold antibodies include Mycoplasma pneumoniae and Epstein-Barr virus. The resulting hemolysis often improves as the infection resolves, although medical monitoring may still be needed.

CAD mainly affects older adults, but it can occur at other ages. It is not contagious and is not generally considered an inherited disease. Cold weather can trigger symptoms, but it does not create the abnormal antibody that causes CAD.

Diagnosis

Diagnosing CAD requires evidence of hemolysis and testing that shows a cold-reacting antibody is involved. Because other conditions can cause anemia or a positive antibody test, results must be interpreted together.

A complete blood count measures red blood cells and hemoglobin. Cold agglutinins can cause red blood cells to clump inside the laboratory tube, producing misleading results such as an unusually high average red blood cell size. Warming the sample may correct these measurements.

Blood tests that support hemolysis include an increased reticulocyte count, bilirubin, and lactate dehydrogenase, or LDH. Reticulocytes are young red blood cells released by the bone marrow. Haptoglobin, a protein that binds material released from damaged red blood cells, is often low.

A blood smear may show red blood cell clumping. However, clumping alone does not confirm CAD.

The direct antiglobulin test, also called a direct Coombs test, checks whether antibodies or complement proteins are attached to red blood cells. In CAD, it is usually strongly positive for the complement fragment C3d and negative or only weakly positive for IgG.

A cold agglutinin titer measures how much the blood can be diluted before the antibody stops

causing visible clumping at a low laboratory temperature. A titer supports the diagnosis, but it does not always predict symptom severity. Careful collection and warm handling of the blood sample may be needed to avoid inaccurate results.

Additional evaluation may include blood protein testing, tests for infections, and imaging when another disorder is suspected. A bone marrow biopsy may be used to look for the B-cell population producing the antibody and to distinguish CAD from other blood or lymphatic conditions.

Treatment and management

Treatment depends on the severity of anemia, hemolysis, circulation symptoms, transfusion needs, other medical conditions, and the effect of CAD on daily life. People with mild, stable disease may be monitored without disease-specific medicine.

Reducing cold exposure can limit red blood cell clumping and circulation symptoms. Practical steps include wearing layered clothing, gloves, warm socks, and head coverings. Air-conditioned spaces may also require extra clothing. Wet clothing should be changed promptly.

Medical teams should know about CAD before surgery, an infusion, or a blood transfusion. Patients may need a warm room, warmed intravenous fluids, and measures to maintain body temperature. The blood bank may need to perform compatibility testing at warmer temperatures.

A blood transfusion can be given when medically necessary. CAD is not a reason to withhold urgently needed blood. Transfusions may require coordination with the blood bank and use of an approved blood warmer.

Infections can increase complement activity and trigger more rapid hemolysis. Prompt assessment and appropriate treatment of an infection may help limit a worsening episode. Some patients are advised to take folic acid because the bone marrow uses it to make new red blood cells, but this should be discussed with the treating clinician.

Disease-specific therapies generally work in one of two ways: they reduce production of the abnormal antibody or block the complement pathway that causes hemolysis.

Sutimlimab-jome is a complement inhibitor approved in the United States to decrease the need for red blood cell transfusion due to hemolysis in adults with CAD. It blocks C1s, an early part of the classical complement pathway. This can reduce hemolysis and improve anemia relatively quickly.

Sutimlimab does not remove the B-cell clone that makes the cold antibody. It may not relieve

all cold-induced circulation symptoms because red blood cells can still clump. Its benefits depend on continued treatment. Because complement contributes to protection against certain bacteria, vaccination and infection precautions are required according to the prescribing information.

B-cell-directed treatment may include rituximab, which targets the CD20 protein on B cells. Rituximab may be used alone or, for selected patients, with bendamustine, a chemotherapy medicine. These treatments aim to reduce the cells producing the abnormal antibody. Responses may take time, but they can continue after treatment ends. Combination treatment can have more side effects and is not suitable for everyone.

Corticosteroids such as prednisone often work poorly in CAD and may cause significant side effects if used long term. Removal of the spleen is also generally less effective than it is for some other autoimmune hemolytic anemias because red blood cells in CAD are cleared mainly by the liver. These approaches may still be considered in unusual circumstances after specialist review.

Complications

Ongoing hemolysis can lead to significant anemia and the need for transfusions. Severe anemia may place extra strain on the heart and lungs, especially in people who already have heart or breathing conditions.

Rapid hemolysis can occur during an infection, after major cold exposure, or around surgery if body temperature is not maintained. Hemolysis may also contribute to pigment gallstones over time.

People with CAD have an increased risk of blood clots, including clots in the legs, lungs, or other blood vessels. The individual risk varies and may also depend on age, mobility, other illnesses, and how active the hemolysis is.

Severe cold-related circulation problems can rarely injure skin or other tissue. Treatment side effects may include infusion reactions, infections, or low blood cell counts, depending on the therapy used.

Follow up

CAD is usually monitored by a hematologist. Routine visits may include a review of fatigue, breathing, circulation symptoms, infections, and the effect of the condition on daily activities. Blood tests may track hemoglobin, reticulocytes, bilirubin, LDH, and other signs of hemolysis.

People receiving treatment may need additional monitoring for infusion reactions, infections, treatment effectiveness, and medication-specific side effects. Vaccination plans should be reviewed before complement-blocking therapy when possible.

Contact the treating team promptly for worsening fatigue, new jaundice, dark urine, fever, increasing shortness of breath, or a clear change in cold-related symptoms. These findings may need timely blood tests but are not always an emergency.

Seek emergency care for:

- Severe difficulty breathing, chest pain, fainting, or confusion
- Sudden weakness on one side, trouble speaking, or other possible stroke symptoms
- Coughing up blood or sudden shortness of breath that could suggest a lung clot
- A cold, painful body part that remains blue, very pale, or numb after gentle warming
- Rapidly worsening weakness or symptoms of severe anemia

Sources

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