Cold Agglutinins

Synonyms: cold agglutinin disease (CAD), cold antibody disease, cold-induced autoimmune haemolytic anaemia

See also separate related article Haemolytic Anaemia.

Cold agglutinins are autoantibodies that react with antigens on the red blood cell surface. They may induce complement-mediated haemolysis and agglutination (clumping) of red cells (a cryopathic haemolytic syndrome). Cold agglutinins exert their pathological effects via haemolysis and red cell destruction in the reticuloendothelial system, predominantly in the liver, or by agglutination of red cells in peripheral cold-exposed vessels leading to vaso-occlusion.

Cold-antibody types of autoimmune haemolytic anaemia include primary chronic cold agglutinin disease (CAD) and rare cases of cold agglutinin syndrome (CAS) secondary to cancer or acute infection.[1]

Cold agglutinins derive their name from the fact that they show maximal activity at temperatures lower than normal body temperature. They are present in low titres in healthy individuals, but may be associated with a range of disease states.

- 'Physiological' cold agglutinins develop as a result of the change in expression of red cell antigens that occurs naturally after birth, and react maximally at about 4°C.
- 'Pathological' cold agglutinins are maximally reactive at around 28-31°C and tend to occur at very low titres. They are most commonly of the immunoglobulin M (IgM) class but can occur less commonly as IgG and IgA forms.

The cold agglutinin-induced diseases are classified into primary or idiopathic form, and secondary form, caused by the existence of an underlying disease state.[2] Primary cold agglutinins are monoclonal; secondary ones may be either polyclonal or monoclonal.[3]

Epidemiology

Primary CAD accounts for 13-15% of autoimmune haemolytic anaemias.[4]

Aetiology

Either primary (idiopathic) form, or secondary to the following conditions:

<table>
<thead>
<tr>
<th>Infective</th>
<th>Haematological/neoplastic</th>
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<tr>
<td>Mycoplasma pneumoniae</td>
<td>Lymphoma</td>
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<tr>
<td>Infectious mononucleosis</td>
<td>Waldenström's macroglobulinaemia</td>
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<td>HIV</td>
<td>Chronic lymphocytic leukaemia</td>
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<td>Influenza</td>
<td>Lymphoproliferative disorders</td>
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<td>Cytomegalovirus</td>
<td>Kaposi's sarcoma</td>
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<tr>
<td>Rubella</td>
<td>Malignancy of any cause may rarely be associated</td>
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<tr>
<td>Chickenpox</td>
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<tr>
<td>Mumps</td>
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<tr>
<td>Infective endocarditis</td>
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<td>Malaria</td>
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<td>Syphilis</td>
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Presentation[2]

Symptoms
- Cold agglutinins may be detected when a routine sample is sent for red blood cells and the results indicate that agglutination is occurring, prompting further tests within the haematology laboratory. It is thought that many people who develop 'pathological' cold agglutinins remain asymptomatic or become only subclinically unwell.
- Where the illness is more severe and chronic it can cause discomfort and purplish discolouration affecting the fingers and toes and other extremities, such as the nose and earlobes. This usually occurs after being out in the cold and so tends to be worse during the winter.
- If haemolysis is significant enough to cause anaemia then nonspecific symptoms such as fatigue and dyspnoea may occur. In patients with angina or cardiac failure, it may cause decompensation of these illnesses.
- If the disease occurs due to pulmonary mycoplasma infection then it may be associated with dyspnoea and cough.
- In severe cases, marked intravascular haemolysis can cause haemoglobinuria and the passage of dark urine after cold exposure.
- Raynaud's phenomenon is usually only a feature of severe cases.
- Nonspecific weight loss, anergy and lymphadenopathy may occur in mild, chronic cases, or as a result of an underlying cause for the problem - eg, lymphoma, and infectious mononucleosis.
- A rare presentation of CAD can occur after blood cooling used with cardiopulmonary bypass for thoracic surgery.[5]

Signs
- Anaemia due to haemolysis may cause pallor affecting the skin, mucous membranes, conjunctivae and palmar skin creases.
- If the patient presents shortly after being out in the cold, then acrocyanosis (purplish discolouration of the distal limbs, fingers and toes) may be found. The same is true for the earlobes, forehead and nose.
- Rarely, in severe cases, there is peripheral skin infarction and necrosis with ulcer formation.
- The presence of splenomegaly, hepatomegaly and/or jaundice is unusual in the primary form and suggests an underlying haematological disorder.
- Lymphadenopathy or fever suggests a haematological or infective precipitant.
- The chest should be examined to check for signs of pulmonary consolidation due to pulmonary mycoplasma infection.

Differential diagnosis
- Warm antibody-mediated haemolytic anaemia and drug-induced haemolysis.
- Cryoglobulinaemia (may present with Raynaud's phenomenon but does not show haemolytic features).
- Paroxysmal cold haemoglobinuria (PCH) - severe CAD can cause haemoglobinuria. PCH is primarily a disease of children and is usually very severe, whereas CAD is more commonly found in older adults and tends to be a mild or subclinical problem.
- Lymphoid neoplasm.
- Other causes of Raynaud's phenomenon - eg, rheumatoid arthritis, progressive systemic sclerosis.
- Severe thrombocytopenia, particularly heparin-induced (can present with sore fingers).
- Vasculitides.
- Severe sepsis without cold agglutinin-mediated haemolysis.

Investigations[2]
- FBC and peripheral smear with reticulocyte count (elevated in active haemolysis).
- Urinalysis and urine microscopy for red cells to distinguish haematuria from haemoglobinuria (the sample must be fresh, as decaying red cells will release haemoglobin).
- Serum globulins and serum protein electrophoresis/immunoelectrophoresis (NB: the sample must be kept at 37°C en route to the laboratory to avoid antibody agglutination and a false negative result).
- Plasma lactate dehydrogenase (LDH) (raised in haemolysis), total and direct bilirubin to confirm/refute haemolysis.
Consider urine electrophoresis to detect Bence-Jones' protein ± 24-hour urine collection for Ig light chains. These tests are usually needed only if there is abnormality in serum globulins.

- More specialised investigations, such as Coombs' test, cold-agglutinin titres, Donath-Landsteiner Ab, cryoglobulins, etc, will usually be performed under haematological guidance and need expert interpretation; bone marrow/lymph-node biopsy may also be conducted in secondary care if necessary.
- Consider specific antibody titres to possible infective triggers - eg, mycoplasma, influenza.
- If collagen-vascular disease is possible, perform autoantibody tests according to the suspected underlying syndrome.
- CXR if mycoplasma is suspected.
- Abdominal ultrasound or CT scan if suspected hepato/splenomegaly or lymphadenopathy is detected.

Management [2]

General principles
- The majority of primary cases require no specific therapy other than wearing warm clothing and taking cold-weather precautions.
- Specialist anti-cold clothing may be needed in severe cases.
- If it is firmly established that there is no underlying cause then the patient should be reassured that the condition is benign and usually resolves, but may be prone to relapses.
- It is wise to follow up patients with idiopathic disease in the long term in the haematology clinic, as some may later show evidence of a previously covert underlying cause.
- Underlying causes should be treated in conjunction with advice from a relevant specialist along with haematological input.
- Postinfective illness tends to resolve and not return.
- Anaemia needs only to be treated by transfusion in extreme, severe cases with very low haemoglobin.
- Plasmapheresis removes the offending antibodies from the circulation and may be used in life-threatening cases.

Pharmacological
- Folic acid supplementation should be prescribed during active, symptomatic phases of the disease to ameliorate the effects of haemolysis, in an attempt to prevent significant anaemia.
- Corticosteroids should not be used to treat CAD. Patients may respond to rituximab monotherapy.
- Fludarabine-rituximab combination therapy is very effective but drug toxicity may be a problem. [4]
- If an underlying haematological neoplasm is found it will usually require antineoplastic therapy according to current therapeutic guidelines. Rituximab, an anti-CD 20 monoclonal antibody, has been successfully used in the treatment of cold agglutinin disease. [6]

Complications
All complications are rare but include:

- Haemolytic crisis following cold exposure or cardiopulmonary bypass.
- Ischaemic necrosis of extremities following prolonged cold exposure.
- Severe symptomatic anaemia.
- Development of malignant disease in a patient initially thought to have a primary form.

Prognosis
Prognosis is very good for primary cases. Postinfective cases usually resolve without problems. Those with an underlying non-infective cause have a life expectancy determined by the nature of the disease in question.

Prevention
- The effects of the cold on sufferers can be reduced through education, appropriate clothing and precautions.
- Folic acid supplementation for active haemolysis.
- Moving to a warmer climate may be advisable for patients who suffer prolonged, severe effects.

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