CONDITION

Cryoglobulinemia

Cryoglobulinemia is the presence of abnormal blood proteins that can clump in the cold and sometimes inflame or block blood vessels.

WHAT IT IS
Cold-sensitive blood proteins that may damage blood vessels

BODY SYSTEM
Immune system, blood vessels, kidneys, nerves, and skin

MAIN SYMPTOMS
Purple spots, joint pain, weakness, numbness

WHAT CAUSES IT
Blood disorders, infections, autoimmune conditions, or unknown causes

HOW IT IS DIAGNOSED
Warm-handled cryoglobulin blood testing and protein typing

MAIN TREATMENT
Treating the cause, immune therapy, or plasma exchange

CAN IT BE CURED?
Sometimes - treating the cause clears cryoglobulins

IS IT AN EMERGENCY?
Sometimes - organ damage or blocked blood flow

LONG-TERM OUTLOOK
Often manageable, but organ involvement can be serious

Overview

Cryoglobulinemia means that proteins called cryoglobulins are present in your blood. These proteins clump together when cooled below normal body temperature and dissolve again when warmed.

Some people have cryoglobulins without symptoms. Others develop cryoglobulinemic vasculitis , in which clumped proteins and immune reactions inflame small or medium-sized blood vessels. This can reduce blood flow and damage the skin, nerves, joints, kidneys, or other organs.

Cryoglobulinemia is grouped into three types according to the proteins involved.

Type I contains one abnormal antibody protein, called a monoclonal immunoglobulin. It is

usually linked to a condition affecting antibody-producing blood cells. The protein may thicken the blood or block small blood vessels.

Types II and III , known as mixed cryoglobulinemia, contain combinations of antibodies that form clusters called immune complexes. These clusters can settle in blood vessel walls and cause inflammation. Mixed cryoglobulinemia is often associated with hepatitis C, certain autoimmune conditions, or blood cell disorders.

Knowing the type matters because treatment is directed at both the symptoms and the underlying cause.

Symptoms

Cryoglobulinemia does not always cause symptoms. When symptoms occur, they may develop gradually, come and go, or worsen during cold exposure.

Common features include:

The purple spots are called purpura . They happen when inflamed small blood vessels leak blood beneath the skin. Spots may appear in repeated outbreaks and can sometimes develop into painful sores.

Kidney involvement may cause blood or protein in the urine. You may notice pink, brown, or foamy urine, swelling around the eyes or ankles, higher blood pressure, or reduced urine output. Early kidney changes may cause no obvious symptoms and be found only through urine and blood tests.

Type I cryoglobulinemia is more likely to cause problems related to reduced circulation. Fingers, toes, ears, or the nose may become unusually pale, blue, painful, or cold. Severe loss of blood flow can damage the skin and tissue.

Less commonly, cryoglobulinemia can affect the lungs, digestive tract, heart, or brain. Symptoms then depend on the organ involved.

- Raised purple or red spots, usually on the lower legs
- Aching or swollen joints
- Tiredness and general weakness
- Numbness, tingling, burning pain, or weakness in the hands or feet

Causes and risk factors

Cryoglobulins are antibodies or antibody-containing protein clusters produced by the immune system. Why they form differs between types.

Type I is usually associated with an abnormal group, or clone, of blood cells making one antibody protein. Related conditions can include monoclonal gammopathy, multiple myeloma, Waldenström macroglobulinemia, or certain lymphomas. A monoclonal gammopathy is an abnormal antibody finding that does not always mean cancer.

Mixed cryoglobulinemia may be linked to long-term infections. Hepatitis C is a major cause worldwide. Hepatitis B, HIV, and some persistent bacterial infections can also be associated with it.

Autoimmune conditions can trigger mixed cryoglobulinemia because the immune system mistakenly reacts against the body's own tissues. Examples include Sjögren syndrome and systemic lupus erythematosus.

Lymphoma and other disorders of antibody-producing B cells may also cause mixed cryoglobulinemia. In some people, no underlying cause is found. This is sometimes called essential or idiopathic cryoglobulinemia.

Cryoglobulinemia itself is not generally inherited. Having one of the associated conditions does not mean you will develop it.

Diagnosis

Diagnosis begins with a blood test for cryoglobulins. The sample must be kept warm from the time it is collected until the serum is separated. If it cools too early, proteins may clump and be removed from the sample, causing a false-negative result.

In the laboratory, the serum is cooled and checked for protein deposits. Any cryoglobulins found are then analysed to determine whether they are type I, II, or III. Testing may include immunofixation, a method that identifies specific antibody proteins.

A negative result does not always rule out cryoglobulinemia, especially if the sample was not handled correctly. Testing may be repeated when symptoms and other findings strongly suggest the condition.

Other tests help identify a cause and look for organ effects. These may include:

A skin or kidney biopsy may be needed if vasculitis or organ damage is suspected. During a biopsy, a small tissue sample is examined under a microscope. This can show blood vessel inflammation and immune protein deposits.

The amount of cryoglobulin in the blood does not always match the severity of symptoms.

Diagnosis and treatment decisions therefore consider symptoms, examination findings, organ tests, and the underlying cause.

- Blood counts and kidney and liver tests
- Urine tests for blood and protein
- Complement levels, especially a protein called C4
- Rheumatoid factor and other autoimmune blood tests
- Tests for hepatitis C, hepatitis B, and HIV
- Tests for abnormal antibody proteins or blood cell disorders

Treatment and management

People who have cryoglobulins but no symptoms or organ damage may not need treatment directed at the cryoglobulins. Follow-up is still important because an associated infection, autoimmune condition, or blood cell disorder may need attention.

When treatment is needed, it is tailored to the type, cause, and organs involved.

For hepatitis C-associated mixed cryoglobulinemia, antiviral treatment can remove the infection and may improve or clear the cryoglobulinemia. Some people with significant blood vessel inflammation or organ damage also need treatment that reduces the harmful immune response.

Immune treatments may include corticosteroids or medicines that target B cells, such as rituximab. These treatments can increase infection risk, so clinicians assess the underlying infection and the severity of organ involvement before choosing an approach.

Type I treatment focuses on the blood cell clone producing the abnormal protein. The treatment category depends on whether the cause is a monoclonal gammopathy, lymphoma, myeloma, or another blood disorder.

Plasma exchange may be used for severe complications, such as very thick blood, rapidly worsening kidney injury, or threatened loss of tissue from blocked blood flow. This procedure removes plasma containing cryoglobulins and replaces it with another fluid. It can lower protein levels quickly, but the effect is temporary unless production of the proteins is also controlled.

Keeping your hands, feet, and body warm may reduce cold-triggered circulation symptoms. It does not remove cryoglobulins or treat blood vessel inflammation.

Complications

Many people do not develop major complications. The risk is higher when cryoglobulins inflame blood vessels, block circulation, or affect an internal organ.

Possible complications include:

Cryoglobulinemia may also be a sign of an underlying blood cancer or persistent infection. Finding that cause is an important part of reducing future risk.

- Chronic skin sores or tissue damage from poor blood flow
- Peripheral neuropathy, causing lasting pain, numbness, or weakness
- Kidney inflammation and reduced kidney function
- Severe high blood pressure related to kidney injury
- Thickened blood, known as hyperviscosity
- Lung bleeding or inflammation
- Reduced blood supply to the intestines, heart, brain, fingers, or toes

Prevention

Cryoglobulinemia often cannot be prevented. It is usually a result of another medical condition rather than something caused by everyday choices.

Preventing hepatitis C infection can prevent some cases of mixed cryoglobulinemia. Measures include not sharing needles or equipment used to inject drugs and ensuring tattooing or piercing equipment is sterile. There is no vaccine for hepatitis C.

Testing and treating hepatitis C can reduce the risk of ongoing immune stimulation, although cryoglobulins or vasculitis may occasionally continue after the virus has cleared.

There is no proven way to prevent cryoglobulinemia caused by an autoimmune condition, monoclonal protein, or blood cell disorder. Avoiding cold may reduce symptoms in some people, especially those with type I, but it does not prevent the condition itself.

Living with it and what to expect

The course of cryoglobulinemia differs according to its type, cause, and effect on your organs. Some people remain free of symptoms and need only monitoring. Others experience episodes of rash, joint pain, tiredness, or nerve symptoms over months or years.

Treating an underlying infection may lead to lasting improvement. However, immune activity can sometimes continue after an infection has cleared. Relapse is also possible, particularly when an autoimmune condition or abnormal blood cell clone remains active.

Kidney or nerve involvement may take longer to improve than a rash or joint pain. Established nerve damage or loss of kidney function may not fully reverse, even after the inflammation is controlled.

Follow-up may include blood pressure checks, urine testing, kidney tests, assessment of skin and nerve symptoms, and monitoring of the underlying condition. Cryoglobulin levels may be followed, but symptoms and organ function are often more useful than the number alone.

Many people can continue working, exercising, and carrying out usual activities. During active symptoms, you may need to adjust activity, protect numb areas from injury, and limit exposure to cold. If fatigue or nerve pain affects daily life, rehabilitation, pain management, or workplace changes may help.

When to get medical help

Arrange routine medical review if you develop repeated purple spots, unexplained joint pain, persistent tiredness, new numbness, or cold-related colour changes in your fingers or toes. These symptoms have many possible causes and need appropriate assessment rather than self-diagnosis.

Seek prompt medical advice for blood or foam in your urine, new swelling, rapidly worsening numbness or weakness, painful skin sores, or a clear drop in urine output.

Get urgent or emergency help for:

These symptoms may indicate blocked blood flow, major bleeding, or serious organ involvement.

- A finger or toe becoming black, severely painful, or persistently blue
- Sudden weakness, facial drooping, speech difficulty, or confusion
- Sudden loss of vision or a severe new visual disturbance
- Chest pain, fainting, or severe shortness of breath
- Coughing up blood
- Severe abdominal pain, especially with vomiting or bloody stool

Common questions

Is cryoglobulinemia a type of cancer?

No. Cryoglobulinemia is an abnormal protein finding and sometimes a blood vessel condition. Type I and some mixed cases can be linked to lymphoma, myeloma, or another blood cell disorder, but many people with cryoglobulinemia do not have cancer.

Does a positive cryoglobulin test mean I have vasculitis?

Not necessarily. Some people have cryoglobulins without inflammation or symptoms. Cryoglobulinemic vasculitis is diagnosed when the proteins are associated with blood vessel inflammation and related clinical findings.

Can cryoglobulinemia go away?

Sometimes. It may clear after successful treatment of an infection or another underlying cause. It can persist or return when the immune trigger or abnormal blood cell clone remains present.

Does cold weather make it worse?

Cold exposure can worsen circulation symptoms, particularly in type I cryoglobulinemia. The name comes from how the proteins behave in a cooled laboratory sample, so not everyone feels worse in cold weather.

Is cryoglobulinemia contagious?

No. Cryoglobulinemia cannot spread between people. An associated infection such as hepatitis C can be transmitted, but the cryoglobulinemia itself cannot.

Can I exercise with cryoglobulinemia?

Many people can exercise if they feel well and have no severe organ involvement. Activity may need to be adjusted during a flare or when nerve damage, skin sores, circulation problems, or kidney or heart involvement is present.

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