CRYOGLOBULINEMIA

What is cryoglobulinemia?

Cryoglobulinemia is a form of vasculitis—a family of rare disorders characterized by inflammation of the blood vessels, which can restrict blood flow and damage vital organs and tissues. In cryoglobulinemia, abnormal blood proteins called cryoglobulins clump together at cold temperatures, restricting blood flow and causing damage to skin, muscles, nerves, and organs—especially the kidneys. More rarely, it can affect the heart, brain, and gastrointestinal tract. Cryoglobulinemia almost always occurs in people who have hepatitis C virus (HCV).

People with cryoglobulinemia may or may not have symptoms. When symptoms are present, they typically include a skin rash with red spots, or a purplish discoloration from bleeding under the skin (purpura); joint or muscle pain; numbness; weakness; fatigue; and breathing difficulties, among others.

Cryoglobulinemia is commonly treated with corticosteroids such as prednisone, and medications that suppress the immune system. Antiviral drugs are prescribed when HCV is present. Left untreated, the disease can cause permanent tissue and organ damage, so it is important to seek prompt medical care when symptoms appear. Relapses can occur, so follow-up care is essential.

Causes

The cause of cryoglobulinemia is not fully understood by researchers. Vasculitis is classified as an autoimmune disorder—a disease which occurs when the body's natural defense system mistakenly attacks healthy tissue. Factors that may trigger the inflammatory process include genetics, medications, infections and viruses, and environmental factors such as pollutants.

While the exact cause of cryoglobulinemia is not known, more than 90 percent of cases are associated with chronic HCV infections, so treating the hepatitis is a major goal of treatment. Cryoglobulinemia is also associated with other underlying inflammatory diseases, including lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and blood cancers such as lymphoma.

Who gets cryoglobulinemia?

Cryoglobulinemia is considered a rare disease. Cryoglobulins are reported in otherwise healthy people, so the actual prevalence of the disease is not known. Prevalence is estimated at approximately 1 per 100,000 worldwide. The disease appears to affect females more than males at a ratio of 3:1. Cryoglobulinemia most frequently affects adults over the age of 50. Internationally, the disease is related to the presence of HCV in a given area and, therefore, varies from country to country. The incidence of HCV in cryoglobulinemia in the Mediterranean region is 90 percent.

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Symptoms

The symptoms of cryoglobulinemia vary depending on the organ systems affected. Some people may have no signs except for elevated cryoglobulin levels detected in a blood test. However, when symptoms are present, they typically include the following:

- Rash with red spots and/or purplish discoloration from bleeding under the skin, mostly affecting the lower legs. Hives may develop, as well as open sores (ulcers) and loss of tissue (necrosis).
- Severe fatigue
- Joint pain
- Numbness, tingling and/or burning sensation of the extremities, especially hands and feet, caused by nerve damage
- Muscle pain and weakness
- Discoloration of hands in cold temperatures
- Swollen lymph nodes
- Abdominal pain
- Kidney damage (Note: A patient can have kidney damage without having symptoms; therefore, patients with vasculitis of any form should have regular urine tests.)

When the brain is involved, a patient may experience headaches or strokes. Heart involvement can cause chest pain and congestive heart failure (difficulty breathing, swelling of the legs).

Diagnosis

In diagnosing cryoglobulinemia, your doctor will consider a number of factors, including a detailed medical history; physical examination; laboratory tests; specialized imaging studies; and, when indicated, a biopsy of an affected tissue or organ. A specific blood test to detect the presence and type of cryoglobulins in the blood will likely be ordered. These results can help determine how best to treat the disease and identify the underlying disease or cause of the condition. All patients with cryoglobulinemia should be tested for HCV.

In addition to blood tests, the following diagnostic tests will likely be ordered:

- **Urinalysis:** To look for blood in the urine, which can indicate kidney involvement
- **Imaging studies:** Chest X-ray; computed tomography (CT) scans of the lungs; MRA, CTA, or angiograms (images of the arteries), as indicated
- **Nerve conduction tests:** Electromyography (EMG) of the arms and legs
- **Biopsy:** Surgical removal and examination of tissue from an affected blood vessel or organ. Bone marrow, skin, liver or kidney biopsy may be ordered, depending on the co-existing disease.

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Treatment

Treatment for cryoglobulinemia depends on organs affected, symptom severity (when there are symptoms), and the underlying conditions. When the co-existing condition is treated, the symptoms of cryoglobulinemia typically improve. For mild cases, doctors may suggest avoiding cold temperatures and treating pain with over-the-counter anti-inflammatory drugs, along with regular check-ups to monitor the disease. For moderate and severe cases, treatments may include the following:

- Antiviral medications are usually prescribed for those with HCV; if doctors determine that HCV is the cause of the cryoglobulinemia, you will likely be referred to a liver specialist (hepatologist).
- Immunosuppressive drugs are the mainstay of treatment for severe disease where vital organs are affected. Corticosteroids such as prednisone, and immunosuppressants such as azathioprine and cyclophosphamide, are widely used.
- The biologic drug rituximab is a common treatment option for this condition. (Biologic medications are complex proteins derived from living organisms; they target certain parts of the immune system to control inflammation.) More research is needed to determine the long-term safety and effectiveness of rituximab for the treatment of cryoglobulinemia.
- Plasmapheresis is an option when patients have life-threatening, or organ-threatening cryoglobulinemia. This procedure filters clumps of cryoglobulins from the blood plasma, helping to prevent cryoglobulins from blocking the arteries and restricting blood flow to organs.

Side effects

The medications used to treat cryoglobulinemia have potentially serious side effects, such as lowering your body's ability to fight infection, and potential bone loss (osteoporosis), among others. Therefore, it's important to see your doctor for regular checkups. Medications may be prescribed to offset side effects. Infection prevention is also very important. Talk to your doctor about getting a flu shot, pneumonia vaccination, and/or shingles vaccination, which can reduce your risk of infection.

Relapse

Even with effective treatment, relapses can occur with cryoglobulinemia. If your symptoms return, or you develop new ones, report them to your doctor as soon as possible. Regular doctor visits and ongoing monitoring are important in detecting relapses and preventing ongoing complications.

Your medical team

Effective treatment of cryoglobulinemia may require the coordinated efforts and ongoing care of a team of medical providers and specialists. In addition to a primary care provider, you may need to see the following specialists: rheumatologist (joints, muscles, immune system); dermatologist (skin); hematologist (blood disorders); nephrologist (kidney disease); hepatologist (liver); cardiologist (heart); neurologist (brain/nervous system); or others as needed.

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The best way to manage your disease is to actively partner with your health care providers. Get to know the members of the health care team. It may be helpful to keep a health care journal to track your medications, symptoms, test results and notes from doctor appointments in one place. To get the most out of your doctor visits, make a list of questions beforehand and bring along a supportive friend or family member if necessary to provide a second set of ears and take notes.

Remember, it's up to you to be your own advocate. If you have concerns with the treatment plan, be sure to speak with the medical team. It is always your right to seek a second opinion.

Living with cryoglobulinemia

Living with cryoglobulinemia can be challenging at times. Fatigue, pain, emotional stress, and medication side effects can take a toll on your sense of well-being, affecting relationships, work and other aspects of your daily life. Sharing your experience with family and friends, connecting with others through a support group, or talking with a mental health professional can help.

Outlook

The outlook for cryoglobulinemia depends on the presence of underlying diseases, the extent of organ damage, and how patients respond to treatment. Some people don't have symptoms and may not need treatment. For those with moderate to severe disease, appropriate and timely treatment can alleviate symptoms, reduce flare-ups, and prevent long-term complications. If permanent damage to nerves or internal organs has not occurred, long-term prognosis is excellent. Because kidney disease is an outcome in some cases of cryoglobulinemia, ongoing monitoring of kidney function is important.

For cryoglobulinemia associated with HCV, effective antiviral therapy usually prevents recurrence of vasculitis. Patients on immunosuppressants should be monitored regularly for side effects.

Clinical studies are ongoing at multicenter research centers, including the Vasculitis Clinical Research Consortium (VCRC), to better understand the risk factors and causes of vasculitis, investigate more effective and safer treatments, and work toward a cure. The Vasculitis Foundation encourages patients to consider participating in clinical research studies to help further understanding of vasculitis. Patients are also encouraged to join the Vasculitis Patient Powered Research Network (VPPRN), where they can provide valuable disease insight and information.

For more information on vasculitis research, visit: www.vasculitisfoundation.org/research

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About Vasculitis

Vasculitis is a family of nearly 20 rare diseases characterized by inflammation of the blood vessels, which can restrict blood flow and damage vital organs and tissues. Vasculitis is classified as an autoimmune disorder, which occurs when the body's natural defense system mistakenly attacks healthy tissues. Triggers may include infection, medication, genetic or environmental factors, allergic reactions, or another disease. However, the exact cause is often unknown.

A Family of Diseases

- Anti-GBM (Goodpasture's) disease
- Aortitis
- Behcet's syndrome
- Central nervous system vasculitis
- Cogan's syndrome
- Cryoglobulinemia
- Cutaneous small-vessel vasculitis (formerly hypersensitivity/leukocytoclastic)
- Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome)
- Giant cell arteritis
- Granulomatosis with polyangiitis (GPA, formerly Wegener's)
- IgA vasculitis (Henoch-Schönlein Purpura)
- Kawasaki disease
- Microscopic polyangiitis
- Polyarteritis nodosa
- Polymyalgia rheumatica
- Rheumatoid vasculitis
- Takayasu's arteritis
- Urticarial vasculitis

About the Vasculitis Foundation

The Vasculitis Foundation (VF) is the leading organization in the world dedicated to diagnosing, treating, and curing all forms of vasculitis. The VF provides a wide range of education, awareness and research programs and services. To learn more, and get the most updated disease and treatment information, visit www.vasculitisfoundation.org

Connect with the VF on Social Media

- Instagram: vasculitisfoundation
- Twitter: @VasculitisFound
- VF Facebook Discussion Group: www.facebook.com/groups/vasculitisfoundation

Ways to Get Involved

- Participate in research
- Join social media

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- Host or participate in an event
- Attend a regional conference and/or symposium
- Give a donation toward long-term solutions
- Become an advocate for yourself, or for others
- Share your journey

Vasculitis Foundation Mission

Building upon the collective strength of the vasculitis community, the Foundation supports, inspires and empowers individuals with vasculitis, and their families, through a wide range of education, research, clinical, and awareness initiatives.

Join the VPPRN!

The Vasculitis Patient-Powered Research Network (VPPRN) seeks to improve the care and health of patients with vasculitis by exploring research questions that matter most to patients, and by advancing medical knowledge about vasculitis. For more information, visit: www.VPPRN.org

The Vasculitis Clinical Research Consortium (VCRC) is an integrated group of academic medical centers, patient support organizations, and clinical research resources dedicated to conducting clinical research in different forms of vasculitis. For more information, visit: www.rarediseasesnetwork.org/cms/vcrc

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