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Cryoglobulinaemia

What is cryoglobulinaemia?

Cryoglobulinaemia is a rare disorder characterised by the presence of abnormal immunoglobulin proteins in the blood that can precipitate out into tissues at low temperatures and causing inflammation and damage.

Immunoglobulins are the class of proteins that make antibodies in response to foreign substances (antigens) introduced into the body. In the case of cryoglobulinaemia, the abnormal immunoglobulins form complexes (cryoglobulins) and precipitate (leach) out of the blood at cold temperatures. This causes restricted tissue blood flow and systemic inflammation, which leads to many clinical signs and symptoms including skin lesions, arthralgia (joint pain), arthritis, [vascular purpura](#) (purple skin marks), [livedo](#) (marbling pattern), and bleeding conditions.

Cryoglobulinaemia often occurs in association with other diseases, particularly autoimmune or infectious diseases (this is known as secondary cryoglobulinaemia). When it occurs without an associated disease it is called idiopathic or essential cryoglobulinaemia.

Types of cryoglobulinaemia

Cryoglobulinaemia is classified into 3 major types based on the make-up of the cryoglobulin complex. Each type has been found to be associated with certain diseases.

Cryoglobulin type	Immunoglobulin composition	Associated diseases
Type I: single monoclonal antibody	Mainly IgM Less often IgG and IgA	Waldenstrom's macroglobulinaemia Chronic lymphocytic leukaemia Multiple myeloma Lymphadenopathy Hairy cell leukaemia
Type II: mixed antibody with monoclonal rheumatoid factor (usually IgG or IgM)	IgM-IgG IgG-IgG IgA-IgG	Waldenstrom's macroglobulinaemia Chronic lymphocytic leukaemia Multiple myeloma Mixed essential cryoglobulinaemia
Type III: mixed antibody with polyclonal rheumatoid factor	IgM-IgG IgG-IgG-IgA	Systemic lupus erythematosus Sjogren syndrome Rheumatoid arthritis Hepatitis A, B or C Systemic sclerosis Vasculitis

Who gets cryoglobulinaemia?

Cryoglobulinaemia is thought to be rare. Essential mixed cryoglobulinaemia occurs in about 1 in 100,000 people. Most cases of cryoglobulinaemia have an underlying cause. The type of cryoglobulinaemia found in patients is roughly 25% with type I, 25% with type II and 50% with type III.

It tends to develop between 40–60 years of age and affect females more than males by 3:1.

What are the clinical features of cryoglobulinaemia?

The clinical features of cryoglobulinaemia differ between the types as shown in the table below.

Features of Type I cryoglobulinaemia	Features of Type II and III cryoglobulinaemia
<ul style="list-style-type: none"> • Acrocyanosis (blueness of the hands and feet from the cold) • Retinal haemorrhage (bleeding) • Severe Raynaud phenomenon • Arterial thrombosis • Gangrene 	<ul style="list-style-type: none"> • Arthralgia and arthritis in the PIP and MCP joints (fingers, hands and toe joints), knees and ankles • Fatigue • Myalgias (muscle pains) • Renal (kidney) immune-complex disease • Cutaneous vasculitis • Peripheral neuropathy (numbness hands & feet)

Skin manifestations of cryoglobulinaemia

Skin problems are almost always present in patients with cryoglobulinaemia.

Skin problem	Type I (%)	Types II and III (%)
Ischaemic necrosis (skin and tissue damage due to lack of blood flow)	40	0–20
Palpable purpura	15	80
Livedoid vasculopathy	1	14 (in type III)
Cold-induced urticaria	15	10 (in type III)
Scarring of tip of nose, pinnae, fingertips and toes		
Nailfold capillary abnormalities		

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Raynaud phenomenon

Other manifestations of cryoglobulinaemia

Many organs may be affected by cryoglobulinaemia.

Affected organ	Signs and symptoms
Lungs	Cough, shortness of breath, fluid in the lungs
Gastrointestinal	Stomach pain, bleeding, enlarged liver and/or spleen
Kidneys	Hypertension (high blood pressure), glomerulonephritis, nephrotic syndrome
Nervous system	Visual disturbances, peripheral neuropathy

Fever may also occur.

What is the treatment for cryoglobulinaemia?

The main aim of therapy is to find and treat the underlying cause, and limit precipitation of cryoglobulins and the inflammation that results. Patients with cryoglobulinaemia should be advised to avoid cold environments to prevent triggering the precipitation of cryoglobulins.

Symptomatic treatment includes:

- Nonsteroidal anti-inflammatory drugs for arthralgia and fatigue.
- Immunosuppressive medications (e.g. [corticosteroids](#), [cyclophosphamide](#), [azathioprine](#)) when there is organ involvement such as vasculitis, renal disease, progressive neurological symptoms and severe disabling skin conditions.
- Plasmapheresis is used for severe or life-threatening complications
- Interferon-alfa combined with ribavirin is effective in patients with hepatitis C associated cryoglobulinaemia.

Identification and treatment of early symptoms such as skin lesions, fatigue or arthralgia, as a result of cryoglobulinaemia, will prevent further organ damage and improve patient outcomes.

Related information

References:

- Book: Textbook of Dermatology. Ed Rook A, Wilkinson DS, Ebling FJB, Champion RH, Burton JL. Fourth edition. Blackwell Scientific Publications.

On DermNet NZ:

- [Livedoid reticularis](#)
- [Sjogren syndrome](#)

Other websites:

- [Cryoglobulinemia](#) - emedicine dermatology, the online textbook

Books about skin diseases:

See the [DermNet NZ bookstore](#)

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DermNet does not provide an on-line consultation service.

If you have any concerns with your skin or its treatment, see a [dermatologist](#) for advice.

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