

Cryoglobulin, Qualitative with Reflex to IFE Typing and Quantitative IgA, IgG, and IgM

IFE-BASED PROCEDURE FOR CRYOGLOBULIN CHARACTERIZATION AND TYPING

Clinical Background

- The term cryoglobulinemia refers to the presence in serum of single or mixed immunoglobulins. These immunoglobulins precipitate at temperatures below 37°C and redissolve at higher temperatures.
- Cryoprecipitation can be observed in a wide spectrum of hematologic, infectious, and immuno-rheumatologic disorders.

Disease Overview

- Monoclonal cryoglobulins have been reported in association with multiple myeloma and other lymphoproliferative disorders, such as Waldenstrom disease.
- Mixed cryoglobulins are composed of two or more different immunoglobulin classes that have been described in various infectious diseases, autoimmune diseases (e.g., SLE, RA, or Sjögren syndrome), and chronic liver disease.
- Cryoglobulins may cause pain, cyanosis, Raynaud phenomenon, vascular purpura, bleeding tendencies, cold-induced urticaria and distal arterial thrombosis with gangrene, and/or skin ulceration upon exposure to cold temperatures.

Epidemiology

- All ages can be affected, but the majority of people affected by cryoglobulinemia are in their 40s or 50s.
- Twice as many women as men have this disorder.

Pathophysiology

- Type I cryoglobulinemia: Monoclonal (type I) cryoglobulins represent 35 percent of the cases of cryoglobulinemia. Type I cryoglobulins are generally associated with multiple myeloma, Waldenstrom disease, or other lymphoproliferative disorders. The clinical problems associated with type I disease occur due to hyperviscosity or concomitant rouleaux formation, and are manifested by cold urticaria, Raynaud phenomenon, cutaneous ulcers, and gangrene of the fingers or toes.
- Type II cryoglobulinemia: Type II cryoglobulins (mixed) with a monoclonal component represent another 25 percent of all cases of cryoglobulinemia. Type II cryoglobulins are associated with both lymphoproliferative and autoimmune diseases. Vascular purpura, Raynaud phenomenon, and articular symptoms are all frequent manifestations of disease.
- Type III cryoglobulinemia: Type III cryoglobulins (polyclonal) are found in autoimmune and infectious diseases. Associated

clinical findings include Raynaud phenomenon, vascular purpura, renal disease, and articular symptoms. In addition, neurologic symptoms are not an uncommon finding in type III disease.

Indications for Ordering

History and symptoms may be suggestive of cryoglobulin disease. These symptoms may include dyspnea, fatigue, glomerulonephritis, joint pain, muscle pain, purpura, Raynaud phenomenon, and/or skin ulceration/necrosis.

Limitations

- Detection of cryoglobulins depends critically on proper specimen collection and handling.
- Improper handling or processing, such as repeated cooling and rewarming of the sample, may lead to reporting of false negative results.

Methodology

- Cryoprecipitation is observed at 2–8°C for 72 hours. Positive precipitate is verified by warming to 37°C; true cryoglobulins will dissolve. Sample will then be reprecipitated in refrigerator.
- Positive samples are analyzed by immunofixation electrophoresis.
- Type I cryoglobulins will show a clear heavy chain with an associated light chain without evidence of polyclonal immunoglobulin in any of the IFE lanes. The cryoglobulin is characterized as a type I cryoglobulin with monoclonal immunoglobulins (e.g., IgG kappa).
- Type II cryoglobulins will show a monoclonal heavy chain (almost always μ), an associated light chain (almost always kappa), and evidence of polyclonal immunoglobulin (almost always IgG). The cryoglobulin is characterized as a type II cryoglobulin with monoclonal immunoglobulins (IgM kappa) and polyclonal immunoglobulins (IgG).
- Type III cryoglobulins will only show trace amounts of polyclonal immunoglobulin. The cryoglobulin is characterized as a probable type III cryoglobulin with trace amounts of polyclonal immunoglobulins (IgG).

Related Test

[Cryoglobulin, Qualitative with Reflex to Quantitative IgA, IgG, and IgM \(2002063\)](#)

References

1. Tedeschi A, et al. Cryoglobulinemia. *Blood Rev* 2007;21(4):183–200.
2. Shihabi ZK. Cryoglobulins: an important but neglected clinical test. *Ann Clin Lab Sci* 2006;36(4):395–408.
3. Sargur R, White P, Egner W. Cryoglobulin evaluation: best practice? *Ann Clin Biochem* 2010;47:8–16.
4. Ferri C. Mixed cryoglobulinemia. *Orphanet J Rare Dis* 2008;3:25.

Test Information

2002403

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.