



Possible Cold Autoinflammatory Syndrome

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Question:

I have a 19-year-old African female patient with hives, facial swelling, shortness of breath, joint pain, low-grade fevers, and joint pain. She thinks these symptoms occur 4 to 5 hours after exposure to cold air. Could this be familial cold autoinflammatory syndrome (FCAS)? She has no symptoms if she holds cold object or drinks cold liquid.

How would one diagnose FCAS?

Response from Phil M. Lieberman, MD:

Thank you for your inquiry.

Yes, based on your description, your patient could certainly have FCAS. This can be confirmed by genetic testing. The first person to describe this disorder and define its underlying pathogenesis was Hal M. Hoffman, MD. I am sending your inquiry to Dr Hoffman for a more detailed response.

Response from Hal M. Hoffman, MD:

The constellation of symptoms you describe is consistent with FCAS except for the shortness of breath, slightly long delay in symptoms, and what I assume is a late age of onset. FCAS is an inherited inflammatory disorder usually due to mutations in the *NLRP3* (*CIAS1*) gene¹⁻³; however, there are some rare cases in which mutations are not identified. There is often a family history, but spontaneous mutations and/or occurrence can be seen. Most patients develop symptoms early in infancy or childhood, although there are rare cases in which patients do not recognize the pattern until young adulthood.

The classic history is a patient who develops painful but sometimes itchy rash on exposed and unexposed areas between 30 minutes and a few hours after a mild cold exposure such as to air conditioning.^{2,4} Other symptoms include extremity swelling, joint and muscle pain, headache, conjunctivitis, fever, and chills. The episodes usually last less than 24 hours. Most patients with

FCAS notice a diurnal pattern, with worsening of symptoms as the day goes on and improvement after a night's sleep. Diagnosis is often made by history alone, especially with a positive family history, but can be confirmed by genetic sequencing for *NLRP3* (Genedx.com).

Other helpful laboratory tests include an chronically elevated C-reactive protein or erythrocyte sedimentation rate and white blood cell count. Antinuclear antibody usually is negative. A negative ice cube test (positive in acquired cold urticaria) is contributory. A skin biopsy specimen of an active lesion that shows neutrophil predominant infiltrate around vessels and sweat glands is also supportive of FCAS. Other cold-induced disorders include familial atypical cold urticaria, now known as PLAID (phospholipase gamma 2 associated immune dysregulation),⁵ but rash develops more acutely and fever is not a feature. These patients can have joint symptoms but usually are associated with autoimmune disease. Some patients also have associated common variable immunodeficiency and granulomatous rash. Classic acquired cold urticaria is another possibility but the history is not consistent.

REFERENCES

1. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein cause familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001;29:301-5.
2. Almeida de Jesus A, Goldbach-Mansky R. Monogenic autoinflammatory diseases: concept and clinical manifestations. *Clin Immunol* 2013;147:155-74.
3. Borghini S, Tassi S, Chiesa S. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an *NLRP12* mutation. *Arthritis Rheum* 2011;63:830-9.
4. Hoffman HM, Wanderer A, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol* 2001;108:615-20.
5. Ombrello MJ, Remmers EF, Sun G, Freeman AF, Datta S, Torabi-Pariz P, et al. Cold urticaria, immune deficiency and autoimmunity due to *PLCG2* deletions. *N Engl J Med* 2012 Jan 26;366(4):330-8.

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