

Familial Cold Autoinflammatory Syndrome

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Abstract

Familial cold autoinflammatory syndrome is an autosomal dominant inherited inflammatory disease characterized by episodes of rash, fever, and joint pain following generalized exposure to cold. Attacks usually occur 1-2 hours after exposure and last less than 24 hours. It has been reported primarily in families from North America and Europe, but sporadic cases have also been reported. The diagnosis is based on clinical presentation and can be confirmed by the identification of a NALP3 mutation. No clinical trials have been performed with FCAS patients, but anakinra, an IL-1 receptor antagonist, has been effective at preventing symptoms prior to a cold challenge and as a maintenance medication in several patients. The NALP3 gene, also known as CIAS1, is expressed in peripheral blood leukocytes and chondrocytes and codes a protein also known as Cryopyrin. NALP3 mutations have also been identified in Muckle Wells syndrome and Chronic infantile neurologic cutaneous articular syndrome. There are several laboratories in Europe and North America where sequencing of NALP3 is performed.

Key-words

familial cold urticaria, CIAS1, cryopyrin, Pypaf1, NALP3, autosomal dominant transmission, inflammatory disorder.

Name of the disease and its synonyms

Familial Cold Autoinflammatory Syndrome (FCAS)

Familial Cold Urticaria (FCU)

Cold Hypersensitivity

Familial Polymorphous Cold Eruption

[Hyper IgD syndrome](#)

[TRAPS](#) (TNF (tumor necrosis factor) Receptor-Associated Periodic Syndrome

FCAS, [Muckle Wells syndrome \(MWS\)](#), and chronic infantile neurologic cutaneous articular ([CINCA](#)) syndrome may represent phenotypes of a single disease as they are all caused by mutations of the same gene

Excluded diseases

This list is not exhaustive

Acquired cold urticaria

[Familial Mediterranean fever](#)

Diagnostic criteria/Definition

Diagnostic criteria have been proposed in order to distinguish FCAS from acquired cold urticaria and other periodic fever disorders.

1. Recurrent intermittent episodes of fever and rash that primarily follow natural, experimental, or both types of generalized cold exposure
2. Autosomal dominant pattern of disease inheritance
3. Age of onset < 6 months
4. Duration of most attacks less than 24 hours
5. Presence of conjunctivitis associated with attacks
6. Absence of deafness, periorbital edema, lymphadenopathy, and serositis

Comments on the differential diagnosis

Four of six criteria are strongly suggestive of FCAS. Conjunctivitis is not as common as initially reported and there are several sporadic cases due to *de novo* mutations.

FCAS primarily is clinical diagnosis, although it is now possible to confirm it in most patients by *NALP3* (*CIAS1*) mutation screening.

The following diseases can be excluded for these reasons:

- Acquired cold urticaria rarely presents in infancy, and does not present with fever and arthralgia. The rash in acquired cold urticaria occurs immediately after direct contact with cold and responds to antihistamines.
- [Familial Mediterranean fever](#) has longer episodes, a different rash, arthritis, and abdominal pain
- [Hyper IgD](#) has longer episodes, a different rash, diarrhea, adenopathies and increased IgD levels.
- [TRAPS](#) (TNF (tumor necrosis factor) receptor-associated periodic syndrome) has longer episodes, a different rash, and periorbital edema

Frequency

FCAS is extremely rare occurring at a rate of less than 1:1,000,000. It has been reported primarily in North America and Europe.

Clinical description

Most patients present at birth or within the first few months of life with rash. Episodes last throughout life and most patients have a normal life expectancy.

Most patients have some rash on a daily basis. However, attacks usually occur following exposures to cold or decreases in temperature including air conditioning and cool damp conditions. The first symptom is rash occurring 1-2 hours after exposure, followed by low-grade fever and arthralgia approximately 4-6 hours after exposure. Other symptoms include

myalgia, conjunctivitis, sweating, drowsiness, headache, extreme thirst, and nausea. Most attacks last less than 24 hours. Renal disease from AA amyloidosis is rare occurring in less than 2% of patients.

There are several patients with clinical overlap with Muckle Wells syndrome (MWS) prompting many investigators to conclude that FCAS, MWS, and chronic infantile neurologic cutaneous articular (CINCA) are merely different phenotypes of a single disease.

Management

Until recently, the mainstay of treatment was supportive with warming treatments and non-steroidal anti-inflammatory drugs. High dose corticosteroids can be effective, but most patients prefer symptoms to the side effects of steroids. Other treatments that have been successful in some cases include anabolic steroids and gold. Recently, several FCAS patients have been treated successfully with anakinra (kineret), a recombinant IL-1 receptor antagonist approved for the treatment of rheumatoid arthritis. While this therapy has not been studied in clinical trials, it has been reported to block symptoms after cold challenge.

Etiology

FCAS is inherited in an autosomal dominant trait; however there are several reported sporadic cases due to *de novo* mutations. The *NALP3* gene (also known as *CIAS1* and *Pypaf1*), localized to chromosome 1q44, was identified and confirmed by several groups. However, there are cases with classic FCAS symptoms that do not possess mutations in *NALP3* suggesting the involvement of additional genes. Additionally, *NALP3* mutations have been identified in patients with MWS and CINCA. The *NALP3* protein is expressed in peripheral blood leukocytes and chondrocytes. It contains a pyrin domain (PYD), similar to the protein pyrin associated with Familial Mediterranean fever (FMF), which is involved in the regulation of inflammation and apoptosis *via* homotypic protein-protein interaction. It also contains a nucleotide binding NACHT domain and several leucine rich repeats, which is similar to several other proteins recently described including Nod2, the protein associated with Crohn's disease and Blau syndrome. *NALP3* appears to bind to the ASC protein, which activates caspase 1, and NFκB leading to downstream cytokine release (including IL-1) and inflammation. It has been proposed that pyrin competes with *NALP3* for ASC. *NALP3* has also been implicated in apoptosis pathways.

Biological diagnostic methods

Sequencing of *NALP3* is available at several centers to confirm the diagnosis, but there are some patients without mutations.

Currently all mutations to date have been identified in exon 3 which codes for the NACHT domain. At least 9 mutations have been reported including V198M, R260W, G301D, L305P, A353V, L353P, A439V, R488K, E627G. Some of these mutations have been associated with Muckle Wells syndrome. (<http://fmf.igh.cnrs.fr/infevers>)

Genetic counseling

The risk for each child born to an affected parent is 50%.

Monitoring of renal function is suggested.

Prenatal diagnosis

It is not indicated.

Unresolved questions and comments

It is still not understood how *NALP3* mutations (including the same mutations) can result in such different phenotypes of FCAS, MWS, and CINCA. There is also no explanation for patients without *NALP3* mutations. It is also not clear how exposure to cold temperatures can elicit attacks. Clinical trials with anakinra have not been performed.

References

Aganna E, Hammond L, Hawkins PN, Aldea A, McKee SA, van Amstel HK, Mischung C, Kusahara K, Saulsbury FT, Lachmann HJ, Bybee A, McDermott EM, La Regina M, Arostegui JI, Campistol JM, Worthington S, High KP, Molloy MG, Baker N, Bidwell JL, Castaner JL, Whiteford ML, Janssens-Korpola PL, Manna R, Powell RJ, Woo P, Solis P, Minden K, Frenkel J, Yague J, Mirakian RM, Hitman GA, McDermott MF. (2003). Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. *Arthritis Rheum*;48:2632-44.

Bertin J, DiStefano PS (2000) The PYRIN domain: a novel motif found in apoptosis and inflammation proteins. *Cell Death Differ* 7:1273-1274

Dode C, Le Du N, Cuisset L, Letourneur F, Berthelot JM, Vaudour G, Meyrier A, Watts RA, Scott DG, Nicholls A, Granel B, Frances C, Garcier F, Edery P, Boulinguez S, Domergues JP, Delpech M, Grateau G. (2002) New Mutations of *CIAS1* That Are Responsible for Muckle-Wells Syndrome and Familial Cold Urticaria: A Novel Mutation Underlies Both Syndromes. *Am J Hum Genet* 70:1498-1506

Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, Teillac-Hamel D, Fischer A, de Saint Basile G. (2002) Chronic Infantile Neurological Cutaneous and Articular Syndrome Is Caused by Mutations in *CIAS1*, a Gene Highly Expressed in Polymorphonuclear Cells and Chondrocytes. *Am J Hum Genet* 71:198-203

Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD (2001a) Mutation of a new gene encoding a putative pyrin-like protein cause familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 29:301-305

Hoffman HM, Wanderer AA, Broide DH (2001b) Familial cold autoinflammatory syndrome: Phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol* 108:615-620

Hoffman HM, Wright FA, Broide DH, Wanderer AA, Kolodner RD (2000) Identification of a locus on chromosome 1q44 for familial cold urticaria. *Am J Hum Genet* 66:1693-1698

Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G. (2001) Association of *NOD2* leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 411:599-603

Inohara N, Nunez G (2001) The NOD: a signaling module that regulates apoptosis and host defense against pathogens. *Oncogene*. 1;20:6473-81.

Johnstone RF, Dolen WK, Hoffman HM (2003) A Large Kindred with Familial Cold Autoinflammatory Syndrome. *Ann Allergy Asthma Immunol* 90:233-237

Kile RL, Rusk HA (1940) A Case of cold urticaria with an unusual family history. *JAMA* 114:1067-1068

Manji GA, Wang L, Geddes BJ, Brown M, Merriam S, Al-Garawi A, Mak S, Lora JM, Briskin M, Jurman M, Cao J, DiStefano PS, Bertin J. (2002) *PYPAF1*: A *PYRIN*-containing *Apaf1*-like protein that assembles with *ASC* and regulates activation of *NF-κB*. *J Biol Chem* 10:10

Martinon F, Hofmann K, Tschopp J (2001) The pyrin domain: a possible member of the death domain-fold family implicated in apoptosis and inflammation.

Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, Chamaillard M, Zouali H, Thomas G, Hugot JP. (2001) *CARD15* mutations in Blau syndrome. *Nat Genet* 29:19-20

Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez

G, Cho JH. (2001). A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 411:603-606

Pawlowski K, Pio F, Chu Z, Reed JC, Godzik A (2001) PAAD - a new protein domain associated with apoptosis, cancer and autoimmune diseases. *Sci U S A* 89:8794-8797

Wang L, Manji GA, Grenier JM, Al-Garawi A, Merriam S, Lora JM, Geddes BJ, Briskin M, DiStefano PS, Bertin J. (2002) PYPAF7: A novel PYRIN-containing Apaf1-like protein that regulates activation of NF- κ B and caspase-1-dependent cytokine processing. *J Biol Chem* 17:17