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 cutanaeous 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

Excluded diseases

This list is not exhaustive
Acquired cold urticaria
Familial Mediterranean fever
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

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 that 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 NFkB 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.

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