

Familial cold autoinflammatory syndrome: Phenotype and genotype of an autosomal dominant periodic fever

Hal M. Hoffman, MD,^a Alan A. Wanderer, MD,^b and David H. Broide, MD^a *San Diego, Calif, and Denver, Colo*

Background: Familial cold autoinflammatory syndrome (FCAS), commonly known as familial cold urticaria, is a rare autosomal dominant inflammatory disorder with episodic symptoms precipitated by exposure to cold.

Objective: The goal of this study was to formulate clinical diagnostic criteria for FCAS in a large cohort in whom the diagnosis of FCAS was supported by genetic linkage to chromosome 1q44.

Methods: We assessed 45 affected and 68 unaffected members from 6 American families. DNA analysis was performed to confirm linkage to chromosome 1q44. Clinical characteristics were determined by means of analysis of detailed questionnaires and medical histories.

Results: Pedigree and genetic analyses confirmed autosomal dominant transmission and linkage to chromosome 1q44 in all families. The most consistent symptoms during attacks were rash (100%), fever (93%), arthralgia (96%), and conjunctivitis (84%). Age of onset was within the first 6 months of life in 95% of affected subjects. The average delay between cold exposure and onset of symptoms was 2.5 hours, and the average duration of an episode was 12 hours. Renal disease with amyloidosis occurs infrequently in FCAS (2%).

Conclusion: The most consistent clinical characteristics of FCAS that discriminate it from other periodic fevers are association with cold exposure, conjunctivitis, age of onset, duration of episodes, and an autosomal dominant inheritance pattern. On the basis of the analysis of genotype and phenotype of FCAS, we formulated clinical diagnostic criteria that can be used to distinguish FCAS from other hereditary periodic fever syndromes. (*J Allergy Clin Immunol* 2001;108:615-20.)

Key words: *Familial cold urticaria, autoinflammatory syndromes, hereditary fevers, amyloidosis, and diagnostic criteria*

Familial cold autoinflammatory syndrome (FCAS), also known as familial cold urticaria, familial polymorphous cold eruption, and cold hypersensitivity (MIM 120100), was first described in 1940 as a rare autosomal

Abbreviations used

ACU: Acquired cold urticaria
ADPF: Autosomal dominant periodic fever
FCAS: Familial cold autoinflammatory syndrome
MWS: Muckle-Wells syndrome

dominant disorder characterized by intermittent episodes of rash, fever, and arthralgia.¹ Although the exact prevalence of FCAS is unknown, approximately 20 different families with FCAS, primarily from Europe and North America, have been reported in the literature.¹⁻²⁰ In this study we objectively identify the clinical characteristics of this syndrome and show that conjunctivitis, previously described in only 3 of 15 reports, is a common symptom. In addition to a comprehensive description of the phenotype, we also provide new genotype information and propose clinical diagnostic criteria.

FCAS has been previously classified as one of the physical urticarias and is frequently compared with the more common cold-induced condition of acquired cold urticaria (ACU). It is important to distinguish between FCAS and ACU because they are not directly related and are distinctly different in their inheritance pattern, age of presentation, natural history, type of cold exposure, timing of symptoms, rash, additional symptoms, laboratory findings, and response to a diagnostic ice cube test (Table I).

The most consistent laboratory finding in patients with FCAS during attacks is polymorphonuclear leukocytosis, with white blood cell counts of up to 36,000/mm³ reported.⁵ Studies with serial white blood cell counts before, during, and after attacks have shown that leukocytosis precedes and accompanies symptoms, with a peak approximately 10 hours into an attack.⁵ Erythrocyte sedimentation rates can be moderately elevated during attacks, as are acute-phase reactants, such as C-reactive protein, α_1 antitrypsin, and haptoglobin.¹⁸ IL-6 and granulocyte colony-stimulating factor were measured in the serum from one patient and shown to be elevated during an attack.²¹ Other laboratory values are within normal limits, and the ice cube test result is negative. Skin biopsies during attacks classically show an intense polymorphonuclear leukocyte infiltrate, with moderate edema in the upper part of the dermis. The inflammatory infiltrate, including neutrophils, eosinophils, and lymphocytes, is concentrated around vascular walls of dilated capillaries.^{16,22} There is no increase in mast cell numbers or tissue histamine levels.^{5,13}

From ^athe Department of Medicine, University of California at San Diego; and ^bthe Department of Pediatrics and Allergy, University of Colorado Health Sciences Center, Denver.

Supported by the National Institutes of Health (NIAID 5-K08 AI01508); the American Academy of Allergy, Asthma and Immunology Education and Research Trust Faculty Development Award; and the Ludwig Institute of Cancer Research.

Received for publication May 10, 2001; revised July 16, 2001; accepted for publication July 17, 2001.

Reprint requests: Hal M. Hoffman, MD, Division of Rheumatology and Allergy/Immunology, University of California at San Diego Mail Code 0635, 9500 Gilman Dr, La Jolla, CA 92093-0635.

Copyright © 2001 by Mosby, Inc.

0091-6749/2001 \$35.00 + 0 1/85/118790

doi:10.1067/mai.2001.118790

TABLE I. Distinguishing features of FCAS and ACU

	FCAS	ACU
Inheritance pattern	Autosomal dominant	Usually sporadic
Age of presentation	Infancy and early childhood	Usually adulthood
Natural history	Throughout life	Often spontaneously resolves within months or years
Cold exposure	Generalized	Local
Onset of symptoms	Usually hours	Minutes
Duration of symptoms	Several hours to days	Minutes to several hours
Rash	Nonurticarial macular papular	Urticaria
Additional symptoms	Fever, arthralgia, and conjunctivitis	Angioedema, wheezing, hypotension
Laboratory findings	Polymorphonuclear leukocytosis	Increased serum histamine
Diagnostic ice cube test	Negative	Positive

Many patients with FCAS are quite incapacitated and have moved to warmer climates in an attempt to reduce the frequency of attacks.¹² Anti-inflammatory agents (sodium aurothiomalate [gold], anabolic steroids [stanozolol], and high-dose corticosteroids) have shown benefit in selected patients.^{10,16,17} In our experience colchicine has no apparent beneficial effect. Because there is no consistently effective treatment, patients with FCAS typically resort to self-remedies, such as sleep and warming treatments, and often must live with chronic intermittent episodes of incapacitation.

FCAS has recently been classified as an autoinflammatory syndrome, a relatively new classification describing conditions in which recurrent inflammatory symptoms occur in the absence of autoantibodies or antigen-specific T cells.²³ FCAS is one of the hereditary periodic fever syndromes, a subgroup of the autoinflammatory syndromes characterized by intermittent attacks of fever associated with rash and arthralgia. These diseases include familial Mediterranean fever, hyper-IgD syndrome, TNF receptor-associated periodic syndrome, Muckle-Wells syndrome (MWS), and other autosomal dominant periodic fevers (ADPFs).^{24,25} However, in the periodic fever syndromes other than FCAS, there is little or no correlation between cold exposure and the onset of symptoms.

We describe the clinical characteristics of 45 subjects with FCAS derived from 6 American families in whom the diagnosis is supported by linkage to chromosome 1q44. Contrary to previous reports on the basis of individual cases or single families, this report is a comprehensive study of a large number of patients with FCAS, allowing for the development of clinical diagnostic criteria distinguishing FCAS from other hereditary periodic fever syndromes.

METHODS

Subjects

Six different American families were recruited through physician referral. Members of families 1, 2, 3, and 6 have been the subjects of previous individual case reports.^{1,7,10,12} A total of 113 subjects were studied (62 male and 51 female subjects), of whom 45 (20 male and 25 female subjects) were affected with FCAS. Ages ranged from 1 to 87 years of age. Multigenerational pedigrees were established for all families to confirm mode of inheritance.

Genotyping

Genomic DNA was isolated, primers for polymorphic short-tandem repeat markers were synthesized, and PCR and automated genotyping were performed, as previously described.²⁰

Clinical assessment

After informed consent was obtained, subjects were evaluated for the presence of clinical characteristics associated with FCAS by using a protocol approved by the University of California-San Diego Institutional Review Board. Detailed medical histories were obtained from all subjects both with and without FCAS. Most were interviewed in person, and subjects not available for face-to-face evaluations were interviewed by telephone. Physical examinations were performed on subjects with FCAS when possible. All subjects completed questionnaires to characterize age of presentation, symptoms during attacks, timing of symptoms in relation to cold exposure, and frequency and severity of attacks. Written answers were compiled and averaged when appropriate. A presumptive diagnosis of FCAS was made on the basis of a history of recurrent episodes of characteristic rash precipitated by cold beginning in early childhood. Environmental cold challenges at temperatures of less than 10°C were performed on 2 affected subjects from families 1 and 3. Skin biopsies were also performed on these probands 3 hours after cold exposure. Diagnosis of FCAS was confirmed by genotyping.

Clinical diagnostic criteria

We developed clinical diagnostic criteria for FCAS on the basis of the phenotype of the affected subjects from 5 families (27 affected and 44 unaffected subjects) that we reported previously in a linkage analysis study.²⁰ The suggested criteria for the diagnosis of FCAS are similar to those proposed for the diagnosis of other hereditary periodic fevers, such as familial Mediterranean fever and familial Hibernian fever.^{26,27} We validated the utility of the criteria by using subjects from family 6 (18 affected and 24 unaffected subjects).

Statistical analysis

Data were expressed as proportions, means, and ranges. Comparisons of proportions were made using the χ^2 test, with an α value of .01.

RESULTS

Autosomal dominant inheritance

All pedigrees demonstrated an autosomal dominant pattern of inheritance of FCAS, with male and female subjects equally affected and with vertical transmission of the disease (Fig 1). Approximately half (53%) of all children with one affected parent were affected, demonstrating complete or near-complete penetrance. No increase in disease severity with each successive generation was seen.

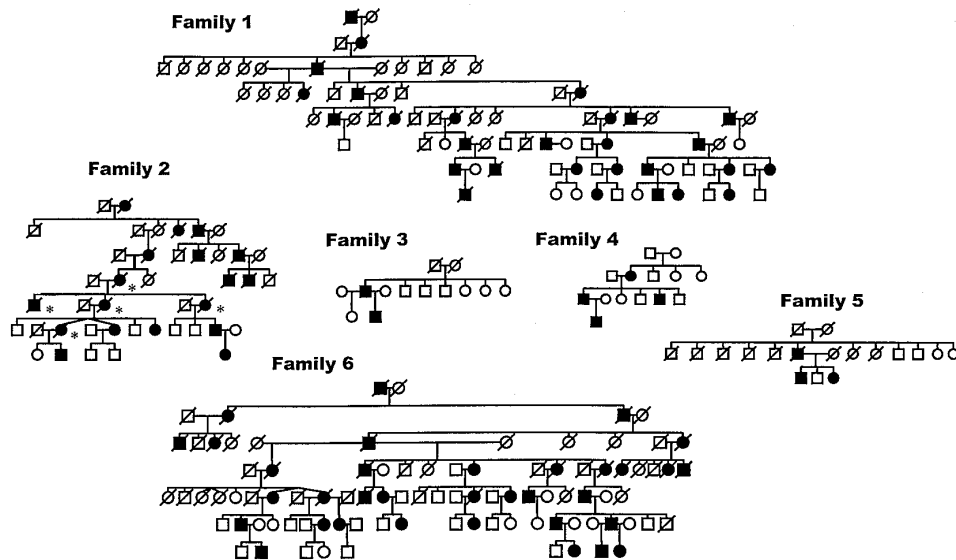


FIG 1. Pedigrees of 6 American families with FCAS. Filled symbols designate affected family members, open symbols indicate unaffected individuals, and asterisks indicate family members with late-onset renal disease. Genetically uninformative individuals were not included.

Linkage to chromosome 1q44

In our previous report we identified a single locus on chromosome 1q44 for all 5 families. Using polymorphic short-tandem repeat markers, we defined a critical region of 10.5 cM at this locus on the basis of observed crossover events that commonly occur during meiosis. This locus was supported by a 2-point lod score of 8.13 and a multipoint lod score of 10.92. All 45 subjects with a presumptive diagnosis of FCAS on the basis of clinical characteristics possessed haplotypes (ordered group of specific marker genotypes in a defined area) on chromosome 1q44 cosegregating with the disease in their family. None of the 68 unaffected family members possessed the affected haplotypes. These haplotypes were specific for FCAS-affected subjects and are not observed in other inflammatory diseases that are not linked to chromosome 1q44.

Age of onset

Age of onset was within the first 6 months of life in 95% of affected subjects and within the first few days of life in 60% of affected subjects. Mean age of presentation was 47 days, with a range of 2 hours to 10 years (Table II). Symptom severity does not appear to vary on the basis of the age of onset.

Clinical characteristics of acute episodes

The recurrent characteristic rash was the most consistent trait occurring in all affected subjects. Additional common symptoms included recurrent fever and chills (93%), recurrent arthralgia (96%), and recurrent conjunctivitis (84%). Other commonly reported symptoms after exposure to cold include profuse sweating (78%), drowsiness (67%), headache (58%), extreme thirst (53%), and nausea (51%, Table III). None of these symp-

TABLE II. Onset and duration of symptoms after cold exposure

	Mean	Range
Age of onset	47 d	2 h-10 y
Cold exposure required to evoke symptoms	52 min	5 min-3 h
Delay of symptoms after cold exposure	2.5 h	10 min-8 h
Length of attacks	12 h	30 min-72 h

toms were reported in unaffected family members, except for in one subject with a diagnosis of rheumatoid arthritis who reported recurrent arthralgia that occasionally worsened with cold exposure.

Dermatologic features

A third of subjects describe the rash as "only itchy," a third describe it as "only burning," and a third describe it as "itchy and burning." The rash presents first on the extremities alone in 45% of subjects, extremities and face in 30%, and extremities and buttocks in 11%. A majority of subjects report generalization of the rash to the remainder of their body during most episodes. Infrequently, subjects reported localized extremity swelling. Skin biopsies on 2 probands performed 3 hours after cold challenge showed neutrophil efflux from vessels and progressive microvascular damage, including endothelial cell swelling, smudging, vacuolization, and near-total luminal obliteration.²⁸

Joint symptoms

Polyarthralgia is one of the most incapacitating symptoms reported by subjects. The most commonly involved joints are hands (88%), knees (68%), and ankles (54%). Other joints involved include feet (42%), wrists (32%), and elbows (24%). Arthritis with joint swelling and ten-

TABLE III. Symptoms after cold exposure in FCAS-affected patients and unaffected relatives

Symptoms during acute episode	FCAS-affected patients from families 1-5, % (n = 27)	FCAS-affected patients from family 6, % (n = 18)	Non-FCAS-affected relatives from families 1-6, % (n = 68)
Rash	100	100	0
Arthralgia	93	100	2
Fever-chill	89	100	0
Conjunctivitis	85	83	0
Profuse sweating	82	72	0
Drowsiness	63	67	0
Headache	56	61	0
Extreme thirst	67	33	0
Nausea	56	44	0

FCAS-affected (families 1-5) versus FCAS-affected (family 6) patients: all nonsignificant at α value of .01.

FCAS-affected (families 1-5) versus non-FCAS-affected patients: all significant at α value of .01.

FCAS-affected (family 6) versus non-FCAS-affected patients: all significant at α value of .01.

TABLE IV. Proposed diagnostic criteria for FCAS

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

The above diagnostic criteria are strongly suggestive of FCAS and are helpful in distinguishing it from other hereditary periodic fevers.

derness was not reported in any of our subjects. Several subjects also reported myalgia.

Ocular symptoms

Ocular symptoms were reported by 84% of affected subjects. Red eyes were the most commonly reported symptom; however, subjects also described increased watering, blurred vision, and ocular pain. Periorbital edema was not reported by any subjects.

Cold exposure required to provoke symptoms

Subjects reported the mean duration of cold exposure required to provoke symptoms was 52 minutes (range, 5 minutes to 3 hours), with symptoms appearing after a shorter exposure at colder temperatures (Table II). Subjects reported a direct correlation between symptom severity and length of cold exposure. The temperature that was required to induce symptoms varied widely, but subjects reported consistently that colder temperatures produced more severe reactions. Many subjects reported more severe symptoms on damp and windy days, and exposure to air conditioning was also reported to be particularly problematic. In 2 probands, symptoms were reproduced by an experimental generalized cold exposure.

Patterns of symptom onset, duration, and severity

Subjects reported the mean time between cold expo-

sure and onset of symptoms was 2.5 hours, with a range of 10 minutes to 8 hours. The initial symptom of an attack was rash in 41% of subjects, joint and muscle pain in 27% of subjects, and chills in 23% of subjects. The average length of an attack was 12 hours, with a range of 30 minutes to 72 hours, and 94% of subjects reported that the majority of their attacks lasted less than 24 hours (Table II). Most subjects reported a daily pattern of fluctuation in symptom severity, with worsening of symptoms in the evening and resolution by morning. There is significant interepisode variability in duration and severity of symptoms. Neither the symptoms nor their severity varied consistently with sex or age. There were no consistent differences in symptom severity between families. In the member of family 2 who had renal amyloidosis, symptoms and severity were not significantly different from those of other subjects.

FCAS and amyloidosis

One 72-year-old affected subject from family 2 had late-onset end-stage renal disease with amyloidosis (confirmed by rectal and renal biopsy). This condition had been reported in at least 4 of her FCAS-affected ancestors (Fig 1) but interestingly was not present in her FCAS-affected monozygotic twin (monozygosity determined by genotyping greater than 20 markers from 3 chromosomes).

Diagnostic criteria

Diagnostic criteria were formulated by using the clinical characteristics of families 1 to 5 (Table IV). By using demonstrated linkage to chromosome 1q44 as the diagnostic standard, all 18 FCAS-affected members from family 6 met 5 of the 6 criteria proposed (14 subjects met all 6 criteria). None of the unaffected subjects from any of the families met more than 1 of the 6 criteria.

DISCUSSION

The data reported in this study confirm that the most consistent symptoms seen in patients with FCAS are recurrent episodes of rash, polyarthralgia, and fever. Ocular find-

TABLE V. Hereditary periodic fever syndromes

Disease	Consistent symptoms*	Length of attacks	Age of onset	Inheritance pattern	Chromosome location	Gene (protein)	Treatments
Familial Mediterranean fever	Monoarticular arthritis, peritonitis, pleuritis, amyloidosis	2-3 d	90%, <20 y	Autosomal recessive	16p13	<i>MEFV</i> (pyrin)	Colchicine
Hyper-IgD syndrome	Polyarthralgia, abdominal pain, lymphadenopathy	3-7 d	96%, <10 y	Autosomal recessive	12q24	<i>MVK</i> (mevalonate kinase)	NSAIDs
TRAPS	Polyarthralgia, abdominal pain, periorbital edema, conjunctivitis, myalgia	>7 d	~80%, <20 y	Autosomal dominant	12p13	<i>TNFRSF1A</i> (p55 TNF receptor)	Corticosteroids Etanercept
MWS	Polyarthralgia, deafness, amyloidosis	2-3 d	~85%, <20 y	Autosomal dominant	1q44	?	NSAIDs?
ADPF	Polyarticular arthritis, conjunctivitis, periorbital edema, amyloidosis	>7 d	?	Autosomal dominant	1q44	?	Colchicine?
FCAS	Polyarthralgia, conjunctivitis	1-2 d	95%, <6 mo	Autosomal dominant	1q44	?	NSAIDs?

*Fever and rash are seen consistently in all of these syndromes. *TRAPS*, TNF receptor–associated periodic syndrome; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

ings are present in 84% of our affected subjects, whereas this symptom was only reported in 3 (7.5%) of 40 previously reported patients with FCAS. Previous studies of the FCAS clinical phenotype defined affected and unaffected individuals solely on the basis of clinical symptomatology. By using a formal symptom survey and confirming the diagnosis with genotyping, we were able to demonstrate consistency in FCAS symptoms among affected individuals and formulate and validate clinical diagnostic criteria (Table IV). Retrospective analysis of several selected clinical reviews showed that 90% of patients with other periodic fever syndromes met 2 or less of the proposed diagnostic criteria for FCAS.^{26,27,29} The proposed diagnostic criteria will require a formal statistical analysis to determine the specificity and sensitivity for differentiating FCAS from other periodic fever syndromes.

As with FCAS, the periodic fever syndromes present with self-limited episodes of fever with synovial and cutaneous inflammation. However, patients with FCAS have not been reported to have serosal inflammation, such as sterile peritonitis or pleurisy, which is often seen in several of the periodic fever syndromes. The duration of symptoms during an episode is another feature that can be used to differentiate these disorders. In FCAS the majority of attacks are less than 24 hours, which is shorter than the duration of episodes in familial Mediterranean fever and MWS (2-3 days), hyper-IgD syndrome (3-7 days), and TNF receptor–associated periodic syndrome (>1 week, Table V).²⁴

The similarities and differences between FCAS and other periodic fever syndromes, especially MWS, are intriguing. In our study one FCAS-affected member of family 2 had renal amyloidosis, a phenotype more consistent with MWS. Late-onset renal disease with amyloidosis was also reported in 2 additional FCAS families.¹⁹ McDermott et al³⁰ recently reported a family from India

with an ADPF, with recurrent prolonged attacks lasting greater than 1 week and characterized by rash, arthralgia, fever, conjunctivitis, and periorbital edema.³⁰ Some of these patients also have AA amyloidosis. Patients with FCAS or MWS have leukocytosis and elevated serum IL-6 levels.^{21,31} Patients with FCAS have symptoms primarily after and proportional to an exposure to cold, but patients with MWS only rarely report onset of symptoms in response to cold exposure.^{32,33} Some patients from the reported family with ADPF have noted worsening of their symptoms with cold exposure.³⁰ One patient with MWS displayed the same daily pattern of symptoms that is commonly seen in patients with FCAS.³¹ Patients with MWS variably express late-onset sensorineural deafness,^{29,31} but none of our patients with FCAS have reported deafness. Although there is a distinct constellation of symptoms that these autoinflammatory syndromes share, the strong correlation between cold exposure and symptoms is unique to FCAS, nerve deafness is unique to MWS, and periorbital edema is unique to the ADPF in the Indian family.

FCAS, MWS, and the ADPF reported in the Indian family have all been genetically linked to chromosome 1q44. We identified linkage of FCAS to chromosome 1q44 in 5 American families²⁰ and confirmed linkage reported in 2 Canadian families and 1 German family.¹⁹ MWS has been linked to chromosome 1q44 in 3 families,³⁴ and the autosomal dominant periodic fever reported by McDermott et al³⁰ was also linked to chromosome 1q44. The phenotype similarity and genetic linkage to the same region may suggest a single gene with different mutations or variable expression caused by genetic or environmental factors. Other possibilities include separate genes that are related and closely linked, microdeletions of different sizes, or variable mutations in a common promoter for 2 or more genes.

The sensitivity to cold, which is unique to FCAS among the autoinflammatory disorders, is a factor in a number of other inflammatory disease processes, such as cryoglobulinemia and ACU. In these diseases it has been proposed that cold temperature affects the molecular assembly of protein complexes,³⁵ such as cryoglobulins,³⁶ skin antigens,³⁷ or autoantibodies.³⁸ Cold exposure has been shown to increase the binding activity of the transcription factor AP-1, which regulates gene expression and causes synthesis of secretory proteins from inflammatory cells.³⁹ Cold can also have direct effects on cellular-mediated immunity by increasing suppressor macrophages that may decrease lymphocyte responses.⁴⁰

Our development of diagnostic criteria on the basis of a comprehensive evaluation of a large cohort will facilitate accurate diagnosis and differentiate between FCAS and other periodic fever syndromes. Our comparison of FCAS with other autoinflammatory syndromes highlights similarities and differences that may reveal underlying molecular and genetic mechanisms of inflammation.

We are extremely grateful to all of the family members who participated in this research effort. We also thank Michael Kaplan, Robert Townley, and Ron Simon for their referral of patients. We thank Sherry Soeffje for editorial support, James Mueller and Kristen Woods for general laboratory assistance, John Weger and Jill Sansone for technical assistance with genotyping, and Richard Kolodner, Webster Cavenee, Michael McDermott, Barrie Ross, and Joel Buxbaum for their helpful advice.

REFERENCES

- Kile RL, Rusk HA. A case of cold urticaria with an unusual family history. *JAMA* 1940;114:1067-8.
- Urbach E, Herrman MF, Gottlieb PM. Cold allergy and cold pathergy. *Arch Dermatol Syphilol* 1941;43:366-74.
- Witherspoon FG, White CB, Hailey H. Familial urticaria due to cold. *Arch Dermatol Syphilol* 1948;58:52-5.
- Rodin HH. Sensitivity to cold. *Arch Dermatol Syphilol* 1951;63:152-5.
- Tindall JP, Beeker SK, Rosse WF. Familial cold urticaria. A generalized reaction involving leukocytosis. *Arch Intern Med* 1969;124:129-34.
- Castelain MP-Y. Urticaire familiale au froid. *Bull Soc Fr Derm Syph* 1971;78:525-6.
- Shepard MK. LLL-Cold Hypersensitivity. In: Bergsma D, ed. *The Third Conference on The Clinical Delineation of Birth Defects, Part 12 Skin, Hair, and Nails*. Baltimore: The Williams and Wilkins Company; 1971.
- Derbes VJ, Coleman WP. Familial cold urticaria. *Ann Allergy* 1972;30:335-41.
- Doeglas HM. Familial cold urticaria. *Arch Dermatol* 1973;107:136-7.
- Vlagopoulos T, Townley R, Villacorte G. Familial cold urticaria. *Ann Allergy* 1975;34:366-9.
- Commerford PJ, Meyers OL. Arthropathy associated with familial cold urticaria. *S Afr Med J* 1977;51:105-8.
- Wanderer AA. An 'allergy' to cold. *Hosp Pract* 1979;14:136-7.
- Martin S, Eastern J, Knox JM. Familial polymorphous cold eruption. *Cutis* 1981;27:173-5.
- Roux H, Gaborit P, Chabrier P, Sayag J, Weiller M. [Familial cold urticaria. Apropos of a case]. *Rev Rhum Mal Osteoartic* 1982;49:131-5.
- Fordyce AM, Coulson IH. Familial cold urticaria—a rare cause of lip swelling. *Br Dent J* 1993;175:417-8.
- Ormerod AD, Smart L, Reid TM, Milford-Ward A. Familial cold urticaria. Investigation of a family and response to stanazolol. *Arch Dermatol* 1993;129:343-6.
- Zip CM, Ross JB, Greaves MW, Scriver CR, Mitchell JJ, Zoar S. Familial cold urticaria. *Clin Exp Dermatol* 1993;18:338-41.
- Kalogeromitos D, Katsarou A, Armenaka M, Polizou E, Zografakis I, Stratigos I. Familial cold urticaria: a father and daughter with typical clinical and laboratory features. *Ann Allergy Asthma Immunol* 1995;74:295-8.
- Jung M, Ross B, Wienker TF, Preuss G, Kuester W, Ries A. A locus for familial cold urticaria maps to distal chromosome 1q: familial cold urticaria and Muckle-Wells-Syndrome are probably allelic [abstract]. *Am J Hum Genet* 1996;59:A223.
- Hoffman HM, Wright FA, Broide DH, Wanderer AA, Kolodner RD. Identification of a locus on chromosome 1q44 for familial cold urticaria. *Am J Hum Genet* 2000;66:1693-8.
- Urano Y, Shikiji T, Sasaki S, Fukuhara K, Arase S. An unusual reaction to cold: a sporadic case of familial polymorphous cold eruption? *Br J Dermatol* 1998;139:504-7.
- Doeglas HM, Bleumink E. Familial cold urticaria. Clinical findings. *Arch Dermatol* 1974;110:382-8.
- Galon J, Aksentijevich I, McDermott MF, O'Shea JJ, Kastner DL. TNFRSF1A mutations and autoinflammatory syndromes. *Curr Opin Immunol* 2000;12:479-86.
- Kastner DL. Familial Mediterranean fever: the genetics of inflammation. *Hosp Pract (Off Ed)* 1998;33:131-4, 139-40, 143-6.
- Drenth JP, van Der Meer JW. Periodic fevers enter the era of molecular diagnosis [editorial]. *BMJ* 2000;320:1091-2.
- Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997;40:1879-85.
- McDermott EM, Smillie DM, Powell RJ. Clinical spectrum of familial Hibernian fever: a 14-year follow-up study of the index case and extended family. *Mayo Clin Proc* 1997;72:806-17.
- Tonnesen MG, Clark RAF, Siegal SL, Reed BR, Capin L, Wanderer AA. Cyclic endothelial cell injury and chronic blood vessel wall alterations in familial cold urticaria [abstract]. *Clin Res* 1985;33:690.
- Muckle TJ. The 'Muckle-Wells' syndrome. *Br J Dermatol* 1979;100:87-92.
- McDermott MF, Aganna E, Hitman GA, Ogunkolade BW, Booth DR, Hawkins PN. An autosomal dominant periodic fever associated with AA amyloidosis in a north Indian family maps to distal chromosome 1q. *Arthritis Rheum* 2000;43:2034-40.
- Gerbis AW, Dahinden CA, Mullis P, Hunziker T. Circadian elevation of IL-6 levels in Muckle-Wells syndrome: a disorder of the neuro-immune axis? *QJM* 1998;91:489-92.
- Black JT. Amyloidosis, deafness, urticaria, and limb pains: a hereditary syndrome. *Ann Intern Med* 1969;70:989-94.
- Berthelot JM, Maugars Y, Robillard N, Pascal O, Stalder JF, David A, et al. Autosomal dominant Muckle-Wells syndrome associated with cystinuria, ichthyosis, and aphthosis in a four-generation family. *Am J Med Genet* 1994;53:72-4.
- Cuisset L, Drenth JP, Berthelot JM, Meyrier A, Vaudour G, Watts RA, et al. Genetic Linkage of the Muckle-Wells Syndrome to Chromosome 1q44. *Am J Hum Genet* 1999;65:1054-9.
- Mitobe J, Mitsuzawa H, Yasui K, Ishihama A. Isolation and characterization of temperature-sensitive mutations in the gene (rpb3) for subunit 3 of RNA polymerase II in the fission yeast *Schizosaccharomyces pombe*. *Mol Gen Genet* 1999;262:73-84.
- Page EH, Shear NH. Temperature-dependent skin disorders. *J Am Acad Dermatol* 1988;18:1003-19.
- Kaplan AP, Garofalo J, Sigler R, Hauber T. Idiopathic cold urticaria: in vitro demonstration of histamine release upon challenge of skin biopsies. *N Engl J Med* 1981;305:1074-7.
- Wanderer AA. The spectrum of cold urticaria. *Immunol Allergy Clin North Am* 1995;15:701-23.
- Turner N, Scarpace PJ, Baker HV, Larochelle JS. AP-1 transcription factor binding activity in rat adrenal medulla and hypothalamus with age and cold exposure. *Neuropharmacology* 1997;36:1065-9.
- Kizaki T, Ookawara T, Izawa T, Nagasawa J, Haga S, Radak Z, et al. Relationship between cold tolerance and generation of suppressor macrophages during acute cold stress. *J Appl Physiol* 1997;83:1116-22.