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Familial Atypical Cold Urticaria: Description of a New Hereditary Disease

Chhavi Gandhi, MD^a, Chris Healy, MD^b, Alan A. Wanderer, MD^c, and Hal M. Hoffman, MD^{a,d,e}

^aDivision of Rheumatology, Allergy, and Immunology, University of California, San Diego, La Jolla, CA

^bUniversity of Wisconsin Health Allergy and Asthma, Madison, WI

^cAllergy and Asthma Consultants of Montana, Bozeman, MT

^dChildren's Specialists of San Diego, Rady Children's Hospital, San Diego, CA

^eSan Diego Branch, Ludwig Institute of Cancer Research, La Jolla, CA

Abstract

Background—Acquired Cold Urticaria (ACU) is usually a self-limited, sporadic, cutaneous disease diagnosed by history and positive cold stimulation time tests (CSTT). We describe three unrelated families (A,B,C) with lifelong atypical cold urticaria, distinguished from ACU and Familial Cold Autoinflammatory Syndrome (FCAS).

Objective—To describe a new hereditary disease of cold urticaria and study its pathogenesis.

Methods—Questionnaires, interviews, physical exams, skin testing and biopsies were obtained. Absolute values, means and prevalence percentages of data are reported.

Results—35 subjects are described with Familial Atypical Cold Urticaria (FACU) (A:17, B:8, C:10) displaying an autosomal dominant (AD) pattern of inheritance. All tested subjects had negative CSTT. Completed questionnaires from family A and B (35) revealed that all affected subjects had lifelong symptoms that began in early childhood with pruritis, erythema and urticaria after cold exposure. Angioedema (A:23%; B:42%), syncope and/or near-syncope (A:46%; B:86%) were also present. Triggers included cold atmosphere (100%), aquatic activities (A:92%, B:100%), handling cold objects (A:54%, B:71%) and ingestion of cold food or beverage (A:69%, B:100%). Skin biopsies demonstrated a mast cell infiltrate with the appearance of degranulation after cold challenge.

Conclusions—FACU is a new cold-induced inherited disease that is different than ACU in its natural history, atmospheric cold elicitation, severity of systemic reactions and CSTT results. FACU differs from FCAS in symptom-timing and the absence of fever, chills and joint pain. The etiology

Corresponding author: Dr. Hal M. Hoffman, 9500 Gilman Drive, Mail code 0635, La Jolla, CA 92093-0635, Phone: 858-534-2108, Fax: 858-534-2110, hahoffman@ucsd.edu.

There is no conflict of interest.

Clinical Implications: FACU patients have negative cold stimulation time tests and precautions and treatment of acute reactions of FACU is similar to acquired cold urticaria.

Capsule Summary: Familial Atypical Cold Urticaria (FACU) is a new disease demonstrating autosomal dominant inheritance that contrasts from other known cold urticarias

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is suspected to be mast cell-related. Treatment of reactions is similar to ACU. Further evaluation of pathogenesis and genetics is warranted.

Keywords

Cold urticaria; autosomal dominant; pedigree; questionnaire; cold stimulation time test; evaporative cooling; skin biopsy; mast cell; antihistamine; epinephrine

Introduction

Cold urticaria is one of the physical urticarias in which patients develop pruritic urticaria and/or angioedema from direct contact with cold, ingestion of cold foods or beverages, handling cold objects, and to a lesser degree, exposure to ambient cold.¹ Patients are at risk for anaphylaxis and cardiovascular collapse, especially when involved with aquatic activities.² Cold urticaria is diagnosed by a suggestive history, physical exam and positive cold stimulation time test (CSTT). A CSTT is positive if cutaneous cold contact, usually with ice, produces a wheal and flare reaction at the time and site of the cold stimulation. Cold urticaria can be divided into acquired forms including acquired cold urticaria (ACU), with a positive CSTT, atypical ACU, with a negative CSTT, and two familial forms including delayed cold urticaria and familial cold autoinflammatory syndrome (FCAS).^{1,3}

ACU is thought to be sporadic and is classified as either primary (usually idiopathic) or secondary (due to cryoglobulinemia, an infectious disease or leukocytoclastic vasculitis).¹ ACU usually affects young adults with a mean duration of disease of 4–5 years with remission or improvement in symptoms in the majority of the patients within 5 years. Atypical ACU has been subdivided into delayed cold urticaria, cold-dependent cholinergic urticaria, cold-dependent dermatographism and systemic cold urticaria.^{1,3} Patients with cold-induced cholinergic urticaria develop generalized punctate urticaria after exercising in cold environments while patients with cold-dependent dermatographism urticate after stroking pre-cooled skin.⁴ Patients with systemic cold urticaria usually have severe urticarial symptoms with a tendency towards generalized systemic reactions after exposure to unique cold conditions.^{1,3,5} Familial delayed cold urticaria is an autosomal dominant (AD) disease characterized by pruritic urticarial-like lesions that develop 9–18 hours after cold stimulation that can resolve into hyperpigmented macules.⁶ CSTT are immediately negative but urtication occurs several hours later at the site of testing.¹ FCAS is an AD disease included in the family of inherited systemic autoinflammatory diseases. With generalized cold exposure, patients develop fever, joint and eye symptoms along with an atypical, nonpruritic, urticarial rash. In affected skin, a neutrophilic infiltration is observed without evidence of mast cell degranulation.⁷

We describe a new familial form of cold urticaria, familial atypical cold urticaria (FACU), in three unrelated multigenerational families. Affected patient presentations do not conform to any one of the atypical ACUs and have distinguishing characteristics from both ACU and FCAS. Similar to ACU, the pathophysiology of FACU is undetermined but our results suggest it to be mast cell-mediated. FACU is a new hereditary cold urticaria and should be considered in patients with a suggestive personal and family history with negative CSTT.

Methods

Clinical assessment

After informed consent was obtained, subjects were evaluated for clinical characteristics associated with atypical cold urticaria by using a protocol approved by the University of California-San Diego Human Research Protection Program. A total of 35 patients (20 affected,

15 unaffected) patients from family A (13 affected, 9 unaffected) and B (7 affected, 6 unaffected) participated. Two affected members of family C were clinically assessed but none participated in the questionnaire. Interviews for family A and B were performed in person, by phone and electronic mail. Physical examinations were performed on subjects when possible. All 35 participating patients (or guardians) completed a 36-point written questionnaire to characterize their clinical features. Written answers were compiled and averaged when appropriate.

Allergy skin prick testing (SPT) was performed with allergen extract for geographical common aeroallergens. Varied durations of cold stimulation time tests were performed with cold contact (ice covered by plastic) over a $5 \times 3 \text{ cm}^2$ area of skin for 3 (6 children), 5 (5 adults), or 10 minutes (2 adults) followed by a 5 minute rewarming period at room temperature. The presence of erythema and/or wheal was recorded. Five adult patients were subsequently immediately tested for cold-induced dermatographism at the site of cold stimulation. Evaporative cooling tests were performed with room temperature tap water placed on patient skin followed by air occlusion for ten minutes and measurement of the reaction. A second drop was placed on the skin and exposed to compressed air and the reaction was recorded. This process was repeated with 100% ethanol.

Punch biopsies of dry, unmoistened skin were performed in sterile fashion on two affected subjects from family B after exposure to room temperature for three hours. The right upper back was prepped and anesthetized with a 0.2cc lidocaine HCl 1% and epinephrine 1:100,000 USP subcutaneous injection. One 4mm punch biopsy was taken from each subject followed by the placement of a single 4.0 nylon suture. The patients were then cold challenged for 15 minutes, in a dry outdoor environment at temperatures of approximately 5°C , with their upper backs exposed. A second biopsy was performed immediately over an erythematous site within 2 cm of the first biopsy, in the same fashion. Normal control samples were obtained after a 30 minute cold challenge at 5°C .

Immunohistochemistry

Skin biopsies were fixed in formalin, embedded in paraffin, sectioned, mounted on slides, deparaffinized and rehydrated before analysis. Sections were subjected to staining with haematoxylin and eosin dyes. Tissue mast cell staining was done with primary mouse monoclonal IgG against tryptase (AbCam) at 1:150 dilution, secondary biotinylated antibody to mouse IgG at 1:200 dilution, peroxidase-labelled avidin detection (Vector ABC PK-6102, Vector Laboratories, Burlingame, CA, USA), and DAB chromagen (DAB Substrate Kit for Peroxidase SK-4100, Vector Laboratories). Haematoxylin was used for counter-staining. Slides were dehydrated and mounted with Cytoseal®. Staining was also performed on three normal control skin biopsy samples.

Statistical Analysis

Data were expressed as means and prevalence percentages of analyzed data.

Results

Pedigree Analysis

Three families A,B,C (see Figure 1), are described with FACU with a total of 35 affected subjects ages ranging from 6 months to 78 years. Each family noted four generations of affected individuals and traced the origin of the symptoms to one ancestor. The families are geographically dispersed (family A: Illinois, Texas, California; family B: Colorado; family C: California, Guatemala), ethnically diverse (families A, B: Caucasian; family C: Hispanic) and not believed to be related to each other. All the families demonstrate an AD pattern of

inheritance. Male and female subjects are equally affected and the vertical transmission rates of the disease for families A (17 affected, 9 female), B (8 affected; 3 female) and C (10 affected; 4 female) are 61%, 62% and 45%, respectively.

Dermatologic features

FACU cutaneous reactions, observed in subjects from all 3 families, included pruritic erythema with urticaria and/or angioedema after direct contact with a cold environment or object. The distribution of the rash appeared to be related to the area of cold exposure and in some circumstances (i.e. swimming) encompassed the entire body. However, localized cutaneous reactions did not generalize. Typical reactions are depicted in Figure 2. Skin exposed to ambient cold (5°C) for 5 minutes developed diffuse erythema and isolated wheal formation (above right brow) of the exposed skin (see Figure 2A). A patient's tear, at room temperature, produced erythema along the line of the teardrop (see Figure 2B) within 1 minute. Skin submerged in warm water did not react, however, when exposed to room temperature air (upper body, arm and face) became pruritic and erythematous (see Figure 2C). This is distinguished from aquagenic urticaria in which immersion into and/or emersion from water should produce urticaria.

Cutaneous Testing

FACU affected patients from all 3 families had negative CSTT and developed erythema without a wheal after 5 minutes of cold contact and 5 minutes of rewarming (see Figure 3A). Similar results were seen with 3 or 10 minutes of testing. Patients were followed for up to 2 hours after the CSTT. Erythema remained for an average of 30 minutes without the development of a wheal reaction and no distant cutaneous reactions occurred from the site of testing (data not shown). One of the 5 adult patients had a positive cold-induced dermatographism test. Patients who were outdoor cold challenged developed erythema and isolated urticarial lesions over skin that was not protected by clothing including their face, neck, upper back, chest and arms. Their cutaneous reactions did not spread and they did not develop any concomitant systemic symptoms. Reactions resolved within 30 minutes of rewarming at room temperature (data not shown).

To further delineate the nature of the patients' cutaneous reactions, evaporative cooling tests were performed. Room temperature water was placed on the skin and covered for 10 minutes. This prevented evaporation and the development of erythema, urticaria and pruritis (see Figure 3B). Exposing the droplet and surrounding skin to compressed air (see Figure 3C) produced erythema only at the site of the droplet. Results were similar with ethanol (image not shown).

A history of atopy (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, asthma or food allergy) was reported in 84% of affected subjects in family A and 14% of affected subjects in family B. Allergy SPT on affected subjects was positive in only 1 of the 6 subjects tested in family B.

Questionnaire Results

Age of onset within the first 6 months of life was reported in 77% and 100% of affected patients from family A and B respectively. Mean age of presentation for family A and B was 3.75 years and 6 months respectively (see Table I), with a range of 6 months to 15 years. All subjects noted a lifelong duration of symptoms and most noted a subjective improvement of the severity of their symptoms after 30 years of age.

While all affected family members noted cutaneous pruritic erythema and urticaria after cold exposure, less than 50% of subjects experienced angioedema (see Table I). Oropharyngeal swelling and/or abdominal pain was triggered by the ingestion of cold foods or beverages in

29% and 43% of family A and B respectively. Both groups also noted syncope or near-syncope at varying degrees (see Table I) that was usually related to their emergence from aquatic activities. Most patients developed their cutaneous symptoms within 5 minutes of cold exposure. The mean symptom duration was 35 minutes (23 minutes; 46 minutes) with a range of 12 minutes to 24 hours depending on the continuation of cold exposure and/or institution of treatment. While no absolute atmospheric temperature was reported to elicit symptoms, humid and cool air was the most reproducible precipitant recorded.

The majority of patients noted that cutaneous drying and warming improved their symptoms within 30–60 minutes (78%; 88%). Antihistamine use was minimal but reportedly provided complete relief and prophylaxis in one individual from family B who was treated with cyproheptadine 30 years ago. After discontinuation because of sedation, the patient's symptoms returned. Multiple members of both families (36%; 50%) used loratadine and/or cetirizine at varying lengths and had a subjective reduction in their symptom severity, mainly pruritis, by 50%. Both families noted antihistamine prophylaxis superior to the treatment of existing symptoms. One subject in Family A also used prophylactic daily montelukast without any significant improvement in her symptoms.

Immunohistochemistry

Skin biopsies were stained for mast cell tryptase. At room temperature, there appeared to be an increased presence of mast cells throughout the dermis and around vasculature in our subjects (see Figure 4A) as compared with normal control skin after cooling (see Figure 4C). After cold challenge, mast cells were present and appeared degranulated in the dermis and around vasculature (see Figure 4B) as compared with control samples after cooling (see Figure 4C).

Discussion

FACU is a newly described familial form of cold urticaria. Data from two families suggest the most consistent symptoms are early onset lifelong localized pruritic erythema with urticaria and/or angioedema after localized or atmospheric cold exposure in patients with a negative CSTT. The presentation of FACU is not consistent with previously described Atypical ACU syndromes. Their lack of symptoms triggered solely by exercise and/or stroking pre-cooled skin help rule-out cold-induced cholinergic urticaria and cold-induced dermatographism, respectively. FACU differs from atypical systemic cold urticaria in that the urticaria is limited to exposed skin without generalization and systemic reactions are not as severe. FACU symptoms occur immediately after cold exposure, in contrast to delayed cold urticaria and its familial form.

FACU, ACU and FCAS do have overlapping characteristics with some distinguishing features (see Table II). FACU patients, like ACU patients, report having cold-induced pruritis and urticaria with the immediate onset of symptoms after cold exposure. FACU patients, in comparison with ACU patients, report a younger age of onset, longer duration of disease, and atmospheric cold as a common trigger. Most importantly, FACU patients have a positive family history and negative CSTT.³ FACU patients, like FCAS patients, appear to be triggered by cold exposure, have lifelong symptoms that begin in early childhood and have an AD pattern of inheritance. Our data on FACU patients suggests, however, that they have more immediate symptoms after cold exposure, and are triggered by the ingestion of cold foods, as compared to FCAS patients. FACU patient also do not report the fever, chills, prolonged rash or extremity pains that are found in FCAS patients.⁷ The proposed diagnostic criteria (see Table III) help discern FACU from both ACU and FCAS. FACU should be considered in any patient who meets all 6 of the proposed diagnostic criteria (see Table III). Our 20 affected participants met

all of the criteria while none of the unaffected subjects met any of the criteria (excluding the negative CSTT).

Evaporative cooling appears to be a significant trigger for the development of cutaneous symptoms in FACU patients. We assume that moist skin, when exposed to air, induces localized cutaneous cooling from the evaporation of the liquid. We suspect that a threshold temperature is reached that triggers the cutaneous symptoms in FACU patients when their skin is moist and exposed to air (room temperature or colder). We presume a similar phenomena occurs in FACU patients who complain of cutaneous symptoms with handling cold objects and oropharyngeal swelling upon ingestion of cold foods, in which the threshold temperature required to produce symptoms is likely warmer than that of the ice cube (CSTT). Further investigations should include effect-based temperature challenge to elicit such a threshold.⁸ Evaporative cooling testing was only performed with room-temperature water and alcohol. Historically, similar reactions were observed in subjects who were exposed to warm water and room temperature air, as with bathing (see Figure 2C). FACU patients do not have aquagenic urticaria, since there was a lack of cutaneous symptoms in our patients whose skin was both immersed in water and tested with occluded water droplets on the skin. Instead, FACU symptoms appear to be related to evaporation and cooling of the skin.

In ACU, the presence of mast-cell mediator release, specifically histamine and eosinophil chemotactic factor, has been documented from peripheral blood during cold challenges.^{9,10} Similarly, the pathogenesis of FACU is suspected to be mast cell-mediated. This is suggested by the appearance of more mast cells in the dermis in our patients at baseline with degranulation after cold challenge, as compared to normal controls. This correlates with the reported successful use of antihistamines for prophylaxis and treatment in some of our subjects.

No formal therapeutic trials have been performed in FACU patients, but a reasonable initial approach includes removal from the stimulus, drying and rewarming the skin and treatment with antihistamines. As with ACU, 1st generation antihistamines,¹ higher doses of 2nd generation antihistamines,¹¹ or combination therapy with a leukotriene receptor antagonist may be required to control symptoms.¹² Daily 2nd generation antihistamines appeared to decrease symptom severity in our patients and may be considered for prophylaxis in other FACU patients. FACU patients, like ACU patients,^{2,13} may be at risk of having life-threatening anaphylaxis, especially when exposed to aquatic activities. They should be advised to avoid aquatic activities and be educated on the possible need for intramuscular epinephrine. Our patients, however, suggested that their milder daily symptoms did not prevent their normal activities if they attempted to stay dry and warm. Educating family members and teachers of children on the expected symptoms of this disease is important to facilitate preparedness and avoid excessive restrictions on activity.

Limitations of this study include data collection via questionnaires, which may include recall bias and inaccuracies, and data collection via phone and/or electronic mail. The number of subjects included in this study was small. Because of geographical constraints, personal interviews and exams were limited. Divergences of symptom prevalence were present between family A and B. This may be due to differences in the family size, phenotypic variability, or environment exposure. CSTT were performed only with ice-cube contact. While CSTT provocation time can be helpful in discerning the severity of a patient's cold urticaria, it does not provide specific triggering temperatures.¹⁴

The genetic basis for most urticarial diseases has not been elucidated. However, the identification of specific mutations in c-kit in patients with systemic mastocytosis¹⁵ and identification of mutations in NLR family, pyrin domain containing 3 (*NLRP3*) in FCAS¹⁶ have led to a better understanding of underlying disease processes and improved treatment.

¹⁷ Future studies include identifying additional families, validating proposed diagnostic criteria, implementing effect-based temperature challenge, and genetic analysis.

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Abbreviations

ACU	acquired cold urticaria
FCAS	familial cold autoinflammatory syndrome
FACU	familial atypical cold urticaria
CSTT	cold stimulation time test
SPT	skin prick test

FIG 1.

Family Pedigrees. **A.** Family A (18 affected; 10 females), **B.** Family B (8 affected; 3 females), **C.** Family C (10 affected; 4 females)

FIG 2.

Cutaneous Manifestations of two affected siblings from Family B (A,B) and one affected child from Family A (C).

A. 16 month old boy after a 5 minute exposure to 5°C atmosphere outdoor exposure followed by 5 minutes at room temperature. **B.** 34 month old boy at room temperature for 2 hours, crying. **C.** 4 year old girl bathing indoors at room temperature.

FIG 3.

Negative CSTT and demonstration of evaporative cooling-induced symptoms. **A.** CSTT performed for 5 minutes with 5 minutes of rewarming without the development of a wheal. **B.** Water droplet after 10 minutes of occlusion without any cutaneous manifestations. **C.** Water droplet after being exposed to compressed air for less than 1 minute with marked erythema and pruritis. Testing with 100% ethanol yielded similar results.

FIG 4. Skin biopsies before and after cold challenge stained for mast cell tryptase. **A.** Patient skin at room temperature for 3 hours with mast cells, with visible granules, throughout the dermis. **B.** Patient skin after 15 minutes exposure to 5°C with mast cells that appear degranulated throughout the dermis and around vasculature. **C.** Unrelated normal control skin after 30 minutes exposure to 5°C.

TABLE I

Clinical characteristics and symptom prevalence of FACU in family A and B; data represents the means of absolute values (age of onset and cold exposure) and prevalence (%).

	Family A (n=13)	Family B (n=7)
Timing		
Mean Age of Onset	3.75 years	6 months
Lifelong duration	100%	100%
Minimum Required Exposure	5 minutes	5 minutes
Characteristics		
Pruritis	100%	100%
Erythema	100%	100%
Angioedema	23%	42%
Burning	23%	57%
Numbness	7%	50%
Syncope/Near Syncope	46%	86%
Triggers		
Cold Atmosphere	100%	100%
Ingestion of Cold Food or Beverage	69%	100%
Handling Cold Objects	54%	71%
Aquatic Activities	92%	100%

TABLE II

Distinguishing features of FACU, ACU and FCAS

	FACU	ACU	FCAS
Inheritance pattern	Autosomal dominant	Usually sporadic	Autosomal dominant
Known genetic mutation	Unknown	Unknown	<i>NLRP3</i>
Onset in early childhood	++	-	++
Lifelong duration	+++	-	+++
Atmospheric cold elicitation	++	+	++
Immediate onset after cold exposure	+++	+++	-
Onset with ingestion of cold foods	++	++	-
Pruritis	+++	+++	+
Respiratory symptoms (bronchospasm)	+	++	-
CV collapse/Syncope	+	++	-
Fever or Chills	-	-	+++
Extremity Pain	-	-	+++
Cold Stimulation Timed Test	-	+++	-
Antihistamines Effective	++	+++	+

+++ Always

++ Most

+ Some

- None

NLRP3: NLR family, pyrin domain containing 3

TABLE III

Proposed diagnostic criteria for FACU

1	Rash: Localized pruritic erythema after cold exposure with urticaria and/or angioedema
2	Autosomal dominant pattern of disease inheritance
3	Rash resolution usually <1 hour after rewarming
4	Absence of fever, chills, or joint complaints
5	Age of onset in childhood with lifelong duration of symptoms
6	Negative cold stimulation timed test (no wheal formation)

The above diagnostic criteria are strongly suggestive of FACU and are helpful in distinguishing it from ACU and FCAS.