

Clinical Features and Anaphylaxis in Children With Cold Urticaria

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ABSTRACT. *Objective.* To characterize the features of cold urticaria in children, with particular focus on systemic reactions, because little pediatric data are available.

Methodology. Chart reviews of 30 children <18 years old who were evaluated in the past 3 years at the Children's Hospital Allergy Program (Boston, MA) and a private allergy practice. Demographic, diagnostic, and therapeutic data were collected. Telephone interviews of patients and/or their parents were performed to obtain follow-up data.

Results. Our data showed that the mean and median ages of onset were ~7 years. No secondary causes were found. One third of patients had anaphylactic reactions. These reactions could not be predicted based on available variables. Patients with negative cold-stimulation test (ice-cube challenge) at 10 minutes had similar symptoms and response to antihistamines as those patients with positive ice-cube-challenge test. In addition, our group of patients with cold urticaria had a strikingly high rate of asthma (46.7%) and allergic rhinitis (50%). The rate of family history of atopic diseases was even higher (89.3%).

Conclusions. Cold urticaria occurs in children and may be associated with anaphylaxis. In our series, no secondary causes were found. All patients with cold urticaria and their parents should be cautioned regarding the risk of anaphylaxis and provided with an epinephrine autoinjector. *Pediatrics* 2004;113:e313–e317. URL: <http://www.pediatrics.org/cgi/content/full/113/4/e313>; *cold urticaria, anaphylaxis, cold-stimulation test.*

ABBREVIATION. H1, histamine 1 receptor.

Cold urticaria is characterized by the development of urticaria and/or angioedema after cold exposure.¹ It is an uncommon form of physical urticaria and thought to be rare in children. Of patients with cold urticaria, >90% have idiopathic (essential) cold urticaria.^{2–4} The remainder are mostly secondary to cryoglobulinemia. A rare form of the disease, known as delayed cold-induced urticaria, is characterized by the delayed expression of

urticaria and angioedema 9 to 18 hours after cold exposure. It is probably inherited as an autosomal dominant condition.⁵ Another syndrome known as familial cold urticaria is characterized by the development of intermittent rash (not urticaria), fever, arthralgia, and conjunctivitis 2.5 hours after generalized exposure to cold. It is inherited as an autosomal dominant condition. Patients with this syndrome were identified recently to have mutations in chromosome 1q44.⁶

The prevalence and course of cold urticaria are not well defined. The most common method to confirm the diagnosis is the ice-cube-challenge test. It entails the application of an ice cube on the skin for non-standardized time intervals followed by a period of rewarming. Approximately 20% of patients with cold urticaria have a negative ice-cube-challenge test.⁴

A serious and interesting feature of cold urticaria is anaphylaxis. It is observed in one third to one half of adult patients.^{3,4,7} Anaphylaxis has resulted in several deaths either directly from the anaphylactic reaction or by drowning when swimming in cold water. This makes it imperative to identify patients with cold urticaria, counsel them and/or their parents, and provide them with an epinephrine autoinjector.

Most information on cold urticaria has been based on adult studies or mixed adult and pediatric studies. Overall, little data are available on children. The aim of our study was to review our experience with children who have cold urticaria. We reviewed epidemiologic features, ice-cube-challenge results, association with other conditions, and response to histamine 1 receptor (H1) antagonists. We also reviewed the course of the disease and focused on patients with systemic reactions (anaphylaxis) and whether they have any predictive factors.

METHODS

Data were collected on 30 children with cold urticaria who had onset of the disease at ≤18 years and were seen within the past 3 years. Fifteen children were followed at the Children's Hospital Allergy Program (Boston, MA), and 15 were evaluated at a private allergy practice. The study was approved by the Children's Hospital Committee on Clinical Investigation.

Cold urticaria was diagnosed based on the patient's history and supported by the ice-cube-challenge test. Our standard protocol for the ice-cube test was the application of an ice cube over the volar surface of the forearm for 5 minutes followed by 5 to 10 minutes of rewarming. The test was interpreted as positive when a wheal appeared over the ice-cube application site. If the test was positive, it was repeated for 3 minutes, and if still positive, it was repeated for 1 minute. If the test was negative at 5 minutes, it was repeated for 10 minutes. This was followed by 5 to 10 minutes of rewarming after each trial. The repetition of the test was done at

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a different site because of local temporary tolerance to cold. If the test was negative after 10 minutes, it was labeled as a negative ice-cube-challenge test.

Symptom severity was categorized into 3 types based on the classification suggested by Wanderer et al,⁴ with the inclusion of respiratory symptoms: type 1, localized urticaria and/or angioedema; type 2, generalized urticaria and/or angioedema without hypotensive or respiratory symptoms; and type 3, severe systemic reactions with ≥ 1 episodes suggestive of respiratory distress (such as wheezing or shortness of breath) or hypotension (ie, dizziness, sensation of fainting, disorientation, or shock).

Data collected for each patient included epidemiologic information, family history, details of the cold-urticaria reactions, ice-cube, blood, and skin tests, and treatment. Blood tests for most patients included cryoglobulins, complete blood count and differential, and erythrocyte sedimentation rate. Some patients had cold agglutinins, complement (CH50, C3, C4), monospot, hepatitis profile, and immunoglobulin levels performed. Patients were treated with various antihistamines. Parents/patients were contacted to follow-up on cold-urticaria progression, response to treatment, development of new allergies, or other family members with the same problem. The assessment of the progression of cold urticaria was generally subjective. It was based on the feeling of the patient and/or patient's guardian as better, worse, or stable according to the severity and frequency of symptoms when they were not on their medications. Disease resolution was defined as no symptoms with swimming and at least during 1 winter season, off of antihistamines. A patient's response to antihistamines was defined as good, moderate, or poor based on the severity and frequency of symptoms while using the medication either as maintenance or as needed for at least 6 months. A variety of antihistamines were prescribed for the patients.

Descriptive statistics (mean, median, and range for continuous variables and proportion for categorical variables) were obtained for each variable. Armitage's trend test with exact *P* value was used to assess relations between the cold-stimulation test and response to H1-antagonists and between cold-stimulation test and cold-urticaria reactions.

RESULTS

Description of patients

This study consisted of 30 cold-urticaria patients: 17 females (56.7%) and 13 males (43.3%). Table 1 gives the patients' age, age of onset, duration, and progression. The median age of the patients was 12 years (range: 2–18.5 years). The median age of onset was 7 years (range: 0.5–14.5 years). The median duration of cold urticaria was 3.2 years (range: 0.5–13.5 years); the mean duration was 4.1 years. Progression data were available for 27 of the 30 patients. The disease resolved in only 2 patients (7.4%): 1 after a duration of 1 year and the other after 3 years. Nine patients (33.3%) improved, and 16 patients (59.3%) did not notice any change (stable). No secondary causes were found.

As also shown in Table 1, 29 of 30 patients had a cold-stimulation test, and 17 (58.6%) were positive. Six patients had the ice cube applied for only 5 minutes rather than the entire 10 minutes and tested

TABLE 1. Demographic Data With Follow-up and Cold-Stimulation Test (CST) Results

Patient No.	Age, y	Gender	Age of Onset, y	Trigger*			Severity of Reaction†	Duration	Progression‡	CST Result§	CST Timing, min
				co	cw	aa					
1	18.5	F	5.0	Y	Y	Y	3	13.5	S	P	5
2	16.0	F	10.0	Y	Y	Y	3	6.0	S	P	3
3	8.5	F	7.0	N	N	Y	3	1.5	NA	N	10
4	5.5	F	4.0	N	N	Y	3	1.5	S	N	10
5	2.5	F	1.5	N	N	Y	1	1.0	S	P	5
6	10.0	M	8.0	N	Y	Y	2	2.0	S	N	10
7	7.0	F	3.5	N	Y	Y	2	3.5	S	N	10
8	16.5	M	12.0	N	Y	Y	1	4.5	B	P	5
9	13.0	M	9.0	N	Y	Y	3	4.0	R	P	10
10	8.5	M	5.5	N	N	Y	2	3.0	NA	P	3
11	14.0	F	6.0	Y	Y	Y	3	8.0	S	P	1
12	6.0	M	1.5	Y	Y	Y	2	4.5	B	ND	ND
13	19.0	F	14.0	Y	Y	Y	3	5.0	S	P	3
14	10.0	F	7.0	Y	Y	Y	2	3.0	S	N	5
15	18.0	F	7.5	N	Y	Y	1	10.5	B	P	3
16	13.0	F	11.0	N	Y	Y	1	2.0	B	N	5
17	14.0	M	7.0	N	N	Y	3	7.0	R	N	5
18	17.0	M	8.0	N	N	Y	2	9.0	B	P	5
19	5.0	M	2.5	N	N	Y	1	2.5	S	P	1
20	11.0	M	6.0	N	N	Y	2	5.0	B	P	3
21	19.0	M	14.5	N	N	Y	2	4.5	B	P	1
22	18.5	F	13.0	N	Y	Y	2	5.5	S	P	3
23	14.0	M	12.0	N	N	Y	2	2.0	S	N	5
24	6.5	M	5.0	N	Y	Y	1	1.5	B	P	3
25	16.0	F	10.0	Y	Y	Y	3	6.0	S	N	10
26	3.0	F	2.0	N	Y	Y	1	1.0	B	N	5
27	13.0	F	11.0	Y	Y	Y	3	2.0	S	N	10
28	7.5	F	7.0	N	Y	Y	2	0.5	S	P	1
29	9.5	M	7.0	Y	Y	Y	3	2.5	S	P	3
30	2.0	F	0.5	N	Y	Y	2	1.5	NA	N	5
Mean	11.4	—	7.3	—	—	—	—	4.1	—	—	5.1
Median	12.0	—	7.0	—	—	—	—	3.2	—	—	5
Range	2.0–19	—	0.5–14.5	—	—	—	—	0.5–13.5	—	—	1–10

* co indicates cold objects; cw, cold weather; aa, aquatic activity.

† 1 indicates localized urticaria and/or angioedema; 2, generalized urticaria; 3, severe systemic reactions with ≥ 1 episodes suggestive of respiratory distress, hypotension, or shock.

‡ Progression was defined as stable (S), better (B), worse (W), or resolved (R). NA indicates that the data are not available.

§ The cold-stimulation test was positive (P), negative (N), or not done (ND).

negative. The percentage of patients who tested positive among the remaining 23 patients was 73.9% (17 of 23).

Swimming was the only trigger for 10 (33.3%) of the 30 patients. Touching cold objects, such as holding a cold cup (in addition to swimming and cold weather), triggered urticaria for 9 patients, whereas cold weather was a trigger (in addition to swimming) for the remaining 11 patients.

Eleven patients (36.7%) experienced systemic symptoms (type 3). Five of these patients (45.5%) had respiratory distress, and 8 (72.7%) had a decrease in their level of consciousness (dizziness, faintness, or hypotension). No vomiting or abdominal pain was reported. Aquatic activity was the trigger in all these patients except for 1, who experienced systemic symptoms with cold-air exposure. No significant differences were identified between this group and the rest of the patients in their cold-stimulation test results or response to antihistamines. The only risk factor identified was a previous history of a systemic reaction to cold exposure.

Of the 30 patients, 6 experienced other forms of urticaria: 1 postviral, 2 chronic idiopathic urticaria, 2 dermatographism, and 1 cholinergic urticaria. Allergen skin testing was performed based on clinical suspicion of environmental allergens. Among 19 patients who had skin testing, 16 (84.2%) were positive for environmental allergens (11 not performed). Three patients (10%) had a family history of cold urticaria in 1 other family member (mother, cousin, and an aunt). These patients did not differ in any epidemiologic aspect, clinical presentation, or laboratory findings. Interestingly, 1 patient has an identical twin who did not have cold urticaria but had allergic rhinitis. Asthma was diagnosed in 14 (46.7%) of the 30 patients, and allergic rhinitis was diagnosed in 15 (50%) of the 30. On the other hand, only 4 of the 30 patients had eczema. There was a high rate of atopy in the patients' families. Of 28 patients who had their family history available, 25 (89.3%) had a family history of atopy.

Relation Between Cold-Stimulation Test and History of Cold-Urticaria Reaction

The frequencies of cold-stimulation test (+/−) versus cold-urticaria reaction (localized hives, generalized hives, or systemic reactions) are shown in Table 2 (the patient who did not have the cold-stimulation test performed had generalized hives).

There were 29.4% localized hives in patients with a positive cold-stimulation test (5 of 17 patients) versus 16.7% in patients with a negative cold-stimulation test (2 of 12 patients) and 35.3% systemic reactions in patients with a positive cold-stimulation test (6 of 17 patients) versus 41.7% in patients with a negative cold-stimulation test (5 of 12 patients); this trend was not significant ($P = .64$, Armitage's trend test). When the 6 patients who had a negative cold-stimulation test at 5 minutes but did not have the test performed for 10 minutes were excluded from analysis, we found that 66.7% (4 of 6) of the patients with a negative cold-stimulation test had systemic reactions, whereas 41.7% (6 of 17) of the patients with a positive cold-stimulation test had systemic reactions; this trend also was not significant ($P = .14$) (Table 2). In reference to cold-stimulation test timing, the sample size in this study was too small to make inferences about its relation to the severity of reactions.

Relation Between Cold-Stimulation Test and Response to Antihistamines (H1-Antagonists)

Responses to antihistamines were available in 24 of the 30 patients (8 had a poor response, 7 had a moderate response, and 9 had a good response). The frequencies of cold-stimulation test (+/−) versus responses are shown in Table 3 (the patient who did not have the cold-stimulation test done had a poor response). There was no clear trend suggesting that patients with a negative cold-stimulation test tend to have poorer response to antihistamines ($P = 1.00$, Armitage's trend test).

DISCUSSION

More than one third of our patients with cold urticaria experienced ≥ 1 systemic reactions. This frequency was similar to most studies performed in adult populations.¹ Consistent with our own findings, cardiovascular symptoms were the most frequent, followed by respiratory symptoms.^{3,4,7} Some studies report significant gastrointestinal symptoms, which we did not observe.^{1,3} The primary determining factors for systemic reactions seem to be the surface area of skin exposed, temperature, and duration of exposure, which might explain why aquatic activity is the most common trigger (rather than cold weather or limited contact with cold objects). Also reported in other series is the development of localized angioedema of the oropharyngeal tract after ingestion of ice-cold water or foods. These patients

TABLE 2. Cold-Stimulation Test (CST) Versus Cold-Urticaria Reaction

	CST	Reaction			Total
		Localized Hives	Generalized Hives	Systemic Reactions	
All subjects	+	5	6	6	17
	−	2	5	5	12
	Total	7	11	11	29
Excluding subjects with negative CST at 5 min	+	5	6	6	17
	−	0	2	4	6
	Total	5	8	10	23

TABLE 3. Cold-Stimulation Test (CST) Versus Response to H1-Blocker

CST	Response to H1-Blocker			Total
	Poor	Moderate	Good	
+	4	5	5	14
-	3	2	4	9
Total	7	7	9	23

are at more risk of having a systemic reaction when swimming.⁷ Because the development of systemic reactions is difficult to predict, some recommend prohibiting all aquatic activities. Patients or their guardians must carry an epinephrine autoinjector to use in the event of anaphylaxis. According to our experience and others, patients with a history of mild reactions (few hives) with swimming often wish to continue participating in aquatic activities and are at low risk for anaphylaxis.⁷ Considerations should include water temperature (preferably >25°C)^{8,9} and supervision by an adult trained in the use of an epinephrine autoinjector. Pretreatment with an antihistamine is recommended, although its effect in preventing systemic reactions is unclear.

The mean duration of illness in our patient population was 4.1 years. Only 2 of 30 patients experienced a complete resolution of their illness. Both patients suffered from cold urticaria for relatively short periods of time, but both had experienced systemic symptoms. They were not different from the remainder of the group, which emphasizes previous reports that it is difficult to predict resolution of symptoms based on any recognized factors. Previous studies report a duration of 4.8 to 9.3 years^{1,7,10} but are limited, as is ours, by the duration of follow-up. A study with long-term follow-up states that the disease resolved in 11% of patients within 5 years and in 26% within 10 years, indicating that cold urticaria is a chronic, persistent condition.¹¹

Most other studies report that cold urticaria begins in young adults (18–27 years old).^{3,4,7,11} Based on this observation, we would have expected a skew in our patient population toward adolescence. Rather, the mean and median ages of onset were ~7 years, which may suggest that cold urticaria occurs earlier in children than was thought and possibly is under-recognized.

The strikingly high rate of personal and family history of atopic disorders is of particular interest. Most studies in the literature showed a prevalence of atopic disorders in patients with cold urticaria that is similar to the general population (~20%).^{3,4,12} Moreover, *in vivo* and *in vitro* studies suggested a different pathophysiology of cold urticaria than asthma, allergic rhinitis, or eczema. One study did find a high rate of atopy among patients with cold urticaria.¹⁰ These observations may indicate some common basic mechanisms between cold urticaria and those conditions. The family histories of atopic disorders may be more accurate in this study, because they were obtained from the affected family members themselves.

In some patients, cold urticaria may be secondary

to an underlying condition,^{2–4} most commonly cryoglobulinemia, which may be primary or secondary. Approximately 4% of cold-urticaria patients will have cryoglobulinemia.^{2,4} On the other hand, 3% of patients with cryoglobulinemia will have cold urticaria.¹³ In several case reports, cold urticaria was associated with infections (such as hepatitis), drug use, cold agglutinins, vasculitis, and malignancy, but no definite causative relationship can be determined. In our patient population, no secondary causes were found, and all screening laboratory tests were normal. With the exception of cryoglobulins, no other screening tests need to be performed.² Laboratory evaluation should be directed by clinical presentation.

The most common method to confirm the diagnosis of cold urticaria is the ice-cube test, as used in our patients. However, the application time of the ice cube is not standardized. Various studies in the literature used different maximum time intervals including 4,¹⁴ 5,¹⁵ 10,^{4,12} 15,² or 20 minutes.^{3,7} Reliable whealing occurs after 10 minutes of rewarming. Previous studies suggest that patients with a shorter duration of cold-stimulation test time (≤ 3 minutes) are more likely to have systemic reactions.^{3,4} On the other extreme, many patients with a negative cold-stimulation test after 10 minutes, identified by some experts to have atypical acquired cold urticaria,⁴ tend to have systemic reactions. We could not demonstrate either of these findings in our patient population, possibly because of the relatively small sample size. Some of the patients were shown to have other concurrent forms of urticaria such as dermatographism as well.¹⁶ Some of the patients who react negatively after 10 minutes of ice-cube application might have a positive reaction if tested for longer periods (15–20 minutes)³ or if they experience a total-body cold-exposure test.¹⁷ In general, patients with a positive cold-stimulation test time ≤ 3 minutes or with a negative cold-stimulation test time ≥ 10 minutes seems to be at more risk of systemic reactions.

Another diagnostic test used by some investigators, especially when the ice-cube test is negative, is immersion of an extremity (usually the forearm) in cold water. This test, again, is not standardized. Different studies report immersion for various time intervals (5–15 minutes) in different water temperatures (4–15°C).^{7,12} Caution must be taken when performing such a test. There are case reports of systemic reactions precipitated by this test, especially in very sensitive patients.¹⁸

The management of cold urticaria is generally frustrating. When this condition is severe and when it is possible, some patients move to warmer climates. Various medications have been used. Because histamine is one of the major mediators in the disease, antihistamines have long been used as a mainstay of therapy. Our experience with children concurs with others. Antihistamines are only modestly effective. In general, antihistamines that are known to be more potent or have broader action were found to be more effective, eg, cyproheptadine, doxepin, or ketotifen,^{19–22} all of which have varying degrees of

sedation as a troublesome side effect. A modest response also occurs for the second-generation, non-sedating antihistamines. Response is also variable among patients. Leukotriene-receptor antagonists generally have not been shown to be effective. In 1 case report, montelukast was found to be effective when antihistamines failed.²³ In another study, systemic corticosteroids were found to be minimally helpful.²⁴

CONCLUSIONS

Cold urticaria is an uncommon form of physical urticaria that is mostly idiopathic. It seems to occur earlier in children than was expected. There is a higher rate of atopy and family history of atopy in those patients. Special attention should be paid to systemic reactions (anaphylaxis) and their prevention. Additional studies are needed to standardize the diagnostic measures, uncover the pathophysiology, and (hopefully) improve therapy.

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