

Cold Urticaria: A Case Report and Review of the Literature

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GOAL

To better manage patients with cold urticaria

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the forms of cold urticaria.
2. Explain the diagnosis of cold urticaria.
3. Discuss the treatment options for patients with cold urticaria.

CME Test on page 240.

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Cold urticaria represents a form of physical urticaria. The disorder is uncommon, and patients with the condition are at risk for systemic reactions and thus must be identified, counseled, and treated accordingly. Diagnosis principally is

clinical and is confirmed by the results of cold stimulation tests such as placing an ice cube on the patient's forearm. Treatment primarily consists of preventive counseling, epinephrine autoinjections, and antihistamines. We present the case of a 9-year-old girl with acquired cold urticaria and review the literature.

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Case Report

An otherwise healthy 9-year-old Filipino girl presented with a complaint of urticaria precipitated by cold exposure over the preceding 5 weeks. She had no recent illnesses and normal results of a school physical examination performed 2 weeks prior to symptom

onset. The patient's medical history was significant only for cat allergy; however, she noted that on multiple occasions, erythema and pruritus appeared on her arms and face after walking through the freezer aisle of a grocery store. Urticaria subsequently developed on regions where she scratched and spontaneously resolved 2 to 3 hours later. On one occasion, urticaria appeared diffusely on the patient while she showered after swimming; it resolved within a few hours after she was given diphenhydramine by her mother. Three days prior to presentation, the patient experienced upper lip angioedema with erythema, globus sensation, and difficulty swallowing after drinking a strawberry slushy. She denied having respiratory complaints at that time, and her symptoms again resolved spontaneously. A day later, the patient tolerated ice cream with no complaints. Her family history was significant for a maternal history of seasonal allergies.

On physical examination, the patient appeared to be well. She had 2 to 3 discrete urticarial lesions on the distal posterior aspect of each calf that, according to her mother, recently began appearing on "cold and rainy" days. The mother attributed them to her daughter's lower legs being exposed because of the length of her pants. Results of the remainder of the examination were unremarkable, and dermatographism was absent.

Laboratory evaluation consisted of a strawberry radioallergosorbent test and cryoglobulins test, both of which had negative results. An ice cube wrapped in plastic was applied to the volar surface of the patient's right forearm for 5 minutes. A 9×6-cm wheal was noted 3 minutes after ice removal (Figure).

A diagnosis of cold urticaria with associated angioedema was made. The patient's mother opted for her daughter to use only diphenhydramine as needed; additionally, an epinephrine autoinjector was dispensed. By 3 months after symptom onset, the patient's only complaint was pruritus of her hands if they became too cold. No urticaria was noted. At 6-month follow-up, the patient denied having had symptoms for the preceding 2 months, and the results of an ice cube test were negative.

Comment

Cold urticaria is a form of physical urticaria that is notable for the development of urticaria and/or angioedema after cold exposure.¹ Cold urticaria syndromes were first described in the 19th century² and are uncommon. However, it has been observed that approximately one third of adult³ and pediatric⁴ patients with cold urticaria have systemic reactions that are mostly hypotensive episodes associated with aquatic activities. Thus, identification of these patients should be a priority.



Wheal formation after an ice cube wrapped in plastic was applied for 5 minutes.

The prevalence of cold urticaria is not well defined. Cold urticaria is most commonly noted in young adults, with only 11% of cases noted in children under 10 years of age.³ Most forms of cold urticaria are idiopathic (Table); however, some forms can be secondary to underlying conditions such as malignancies, vasculitides, and infectious diseases.⁸ Cryoglobulinemia (primary and secondary to malignancy) often is cited as a cause of secondary cold urticaria.^{3,8-11} Mounting evidence indicates that a possible autoimmune mechanism underlies the idiopathic form of this disorder in many patients.¹²

Although most forms of cold urticaria are considered to be acquired, familial forms have been described,^{7,13} some of which have been classified within the hereditary periodic fever syndromes.¹²

Diagnosis of cold urticaria primarily is made by evaluating the patient's clinical history; the diagnosis may be confirmed by applying a cold stimulus, most commonly an ice cube wrapped in plastic and applied to the volar aspect of the patient's forearm. A positive reaction is noted by the formation of a wheal during rewarming of the

Cold Urticaria Syndromes⁴⁻⁷

Cold Urticaria	Diagnostic Features	Treatment	Inheritance
Primary acquired (idiopathic)	Immediate response to cold stimulus test	Avoidance; antihistamines*; epinephrine	No [†]
Secondary acquired (most often cryoglobulinemia)	Immediate response to cold stimulus test; underlying disorder	Avoidance; antihistamines*; epinephrine; treatment of underlying disorder	No [†] Possibly that of underlying disorder
Atypical	Lack of immediate response to cold stimulus test; suggestive history	Avoidance; antihistamines*; epinephrine	Some [‡]
Familial [§]	Family history; associated clinical findings	Depends on specific diagnosis	Yes

*The addition of leukotriene inhibitors also may be of benefit.

[†]A higher rate of atopy in patients with cold urticaria than in the general population has been reported.

[‡]Familial delayed cold urticaria has been described.

[§]Familial cold autoinflammatory syndrome and familial delayed cold urticaria.

skin. The length of time that a cold stimulus is applied is not standardized; commonly, 3-, 5-, and 10-minute applications are used. Visitsuntorn et al¹⁴ observed the effectiveness of 3- or 5-minute applications in children who had not taken antihistamines for at least 5 days prior. The authors also noted that false-positive results (defined as reddening of the skin and minimal edema) were possible with 10- and 20-minute applications in patients with chronic urticaria not induced by cold. Other studies have observed that the length of time necessary for a cold stimulus to induce wheal formation inversely may be related to the patient's risk of having a systemic reaction.^{1,8,12} Specifically, patients who demonstrated wheal formation after the application of a cold stimulus for 3 minutes or less were noted to experience cold-induced hypotension more frequently. Regardless, it should be recognized that all patients with cold urticaria are at risk for hypotensive reactions.

Approximately 20% of patients with cold urticaria lack an immediate response to cold stimulus with an ice cube; these patients have so-called atypical acquired cold urticaria syndromes^{1,12} (eg, cold-dependant dermatographism, delayed cold urticaria, systemic cold urticaria). Other forms of cold stimulus testing that can be considered include partially immersing a limb of the patient's in cold water³ or placing the patient in a cold room¹⁵; however, these forms of cold stimulus may put the patient at increased risk for a systemic reaction.

Finally, scratching the skin prior to cooling or during cooling also may be of diagnostic value in cases of cold-dependant dermatographism.^{9,15}

Additional testing should be guided by a patient's history. To determine if a secondary cause is responsible for the clinical presentation of cold urticaria, laboratory studies could include complete blood count, erythrocyte sedimentation rate, antinuclear antibodies titer, infectious mononucleosis serology, syphilis serology, rheumatoid factor, total complement, cold agglutinins, cold hemolysin, cryofibrinogen, and cryoglobulin.¹² Of note, approximately 4% of patients with cold urticaria have been observed to have cryoglobulinemia. Thus, testing for cryoglobulinemia is the most likely laboratory study to yield positive results.^{1,16} Beyond evaluation for cryoprecipitates, however, an extensive search for etiology is not indicated unless additional clinical findings warrant investigation.¹⁶

Treatment of patients with cold urticaria can be difficult. Patients and their families should be counseled on the risks of aquatic activities and should be instructed on the proper use of an epinephrine autoinjector. In severe cases, patients may elect to move to warmer climates. Antihistamines sometimes provide benefit, especially at high doses and/or with the more potent formulations, such as doxepin. Cyproheptadine has been shown to be more effective than chlorpheniramine.¹⁷ Second-generation antihistamines also may be considered to minimize sedation. Cetirizine, loratadine, and

desloratadine have been shown to be effective and well-tolerated options for treatment.^{18,19} Additionally, leukotriene receptor antagonists may have a role in treatment.⁵ Bonadonna et al⁶ demonstrated that cetirizine and zafirlukast in combination are more effective than either drug alone. Adjusting the level of medication so that the patient requires more than 3 minutes of cold stimulus testing before having a wheal response is a recommended goal of therapy that is aimed at minimizing the patient's risk of having a hypotensive reaction.¹²

Cold urticaria is an uncommon disorder that can put patients at significant risk. Taking a thorough history and confirming the condition through the use of cold stimulation tests can lead to a diagnosis in most cases. Although most forms of cold urticaria are idiopathic and acquired, familial and secondary forms also must be kept in mind when considering this diagnosis. In addition to antihistamine therapy, an epinephrine autoinjector and preventive measures play an important role in treating patients with cold urticaria.

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