

Localized Cold Urticaria to the Face in a Pediatric Patient: A Case Report and Literature Review

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Abstract: We present a curious case of localized cold urticaria restricted to the face in a 10-year-old girl. Testing for the condition using an ice cube was positive only in the facial area. After 2 years, the patient continues to experience localized urticaria only on her face on cold exposure. A review of the available published medical literature on cold urticaria was performed using Ovid and PubMed databases. The literature search was not limited to the English language. Only three other cases of cold urticaria localized to the face were identified. Upon review of the published reports on cold urticaria and discussion of classification and diagnostic testing, we conclude that cold urticaria clearly is a rare and poorly understood entity.

Acquired cold urticaria syndromes include various disorders that can occur on contact with cold air, cold objects, or cold fluids and may be accompanied by angioedema. Although most cases (96%) are idiopathic, cold urticaria has been well documented in association with systemic inflammatory disease; hematologic disease; thyroid disease; infection with such viruses as hepatitis C virus, human immunodeficiency virus, and Epstein–Barr virus; and use of certain medications (e.g., birth control pills, immunotherapy agents).

CASE REPORT

A previously healthy 10-year-old girl presented with erythematous, pruritic, urticarial papules of 8 months' duration that occurred periorally and also involved the adjacent cheek (Fig. 1). The papules had never been

noted to occur elsewhere on her body and occurred almost every time she drank from a water fountain or after she was exposed to cool weather while going to school. The lesions disappeared spontaneously after 10 to 15 minutes. The patient had tried applications of hydrocortisone cream to the affected areas, but no improvement occurred. No associated systemic component, such as angioedema, fever, or myalgia, was linked with these attacks.

The patient's family history was unknown. Her past history was significant for recurrent otitis, tonsillitis, and pharyngitis. Rapid tests for streptococcal infections were negative on many occasions (from 2 to 10 yrs of age with 2–3 episodes per year), except once, when the patient was 6 years old. Various antibiotics—especially, amoxicillin—were prescribed, along with suggestions for acetaminophen or a nonsteroidal anti-inflammatory drug.

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Figure 1. Evanescent, pruritic urticarial papules on cheek and mouth after drinking cold water from fountain.

She did not have testing for thyroid function, hepatitis C, or Epstein–Barr virus. The patient had no history of atopy, asthma, or dermatographism; she had no recent intercurrent illness. Rarely, she took ibuprofen for musculoskeletal pain. On initial examination, no cutaneous eruption was present. She had normal test results for complete blood cell count and C-reactive protein.

The patient was asked to drink from a water fountain in the office, and within 60 seconds, an urticarial erythematous wheal developed near her mouth on the right cheek and in line with the exposure to the flow of water. After a 15-second cold, nonwet stimulation test performed in the office using ice in a plastic bag, the patient immediately developed a wheal-and-flare reaction on the right cheek periorally. This response did not occur with tepid water applied to the same surface. Ice and water applied for 15 seconds to the forearm, abdomen, and neck also failed to induce a lesion. At a subsequent visit, a cold stimulation time test was performed on her forearm at 1, 5, 10, and 20 minutes and was negative at these times and at 24 hours as well. Because of the immediate nature of her reaction and the lack of response to water itself, the patient received a diagnosis of localized, acute cold urticaria.

Cetirizine hydrochloride (10 mg/day) provided significant improvement, but cromolyn sodium (100 mg/5 mL before meals and at bedtime) and loratadine (10 mg/day) did not. The patient continues after 2 years to have the cold urticaria only on her face, even after swimming in a cool body of water.

DISCUSSION

We report a unique case of acute, localized cold urticaria of the face caused by direct contact with ice, cold water, and cold ambient temperature. After extensively searching published reports, we found only three other

cases of localized, acquired cold urticaria that involved the face exclusively.

Case 1 (1)

A 30-year-old patient had a 6-year history of localized urticaria that occurred on the face after exposure to weather that was cold and windy or cold and wet. No other body area was affected. No infection, illness, or food ingestion was related to the episodes, which were not precipitated by iced drinks. An ice cube test (ICT) showed a positive response only at the areas that elicited mention in the prior history; results of ICT on other body areas were negative. The urticaria responded to cetirizine (10 mg/day).

Case 2 (2)

A 47-year-old man presented with localized facial urticaria of 2 years' duration that developed after exposure to cold wind and cold rain. No other portion of his body had similar problems. The ICT result was positive only on his face and neck. The patient responded to cyproheptadine hydrochloride, but on stopping the treatment 18 months later, the urticaria returned.

Case 3 (3)

A 38-year-old patient presented with a 3-year history of both urticaria associated with exposure to cold air and localized angioedema of the scalp associated with hoarseness. These attacks lasted 10 hours. Iced beverages did not induce the condition, and the ICT result was positive on the forehead but negative on the arms, chest, and back. Although treatment with antihistamines failed to control the cold urticaria, cromolyn therapy (400 mg/day) was successful.

COMMENT

An approach to the classification of cold urticarias is presented in Table 1.

In a series of 220 urticaria cases (4), 96% were primary acquired cold-related urticaria (PACU), but only two cases were secondary acquired cold urticaria. No case of localized cold urticaria was observed.

Testing of cases considered to involve physical urticaria, including cold urticaria, is summarized in Table 2. Of the cold urticarial syndromes, PACU is most common. It is of interest that early responders to the ICT (≤ 3 minutes) generally have more severe presentations and have a higher prevalence of systemic symptoms (5). In our patient, urticaria developed after the ICT was

TABLE 1. *Classification of Acquired Cold Urticaria and Familial Cold Urticaria According to Results of ICT and CSTT*

Acquired cold urticaria: positive ICT or positive CSTT
Primary acquired cold urticaria
Secondary acquired cold urticaria
Cryoglobulinemia
Infectious diseases
Hypersensitivity vasculitis
Miscellaneous acute cold urticaria caused by insect stings, medications, neoplasms
Atypical acquired cold urticaria: 20% of cases with atypical CSTT; may involve mean decrease in body temperature
Systemic acquired cold urticaria
Cold-dependent dermatographism: urticaria after stroking precooled skin but negative ICT
Cold-induced cholinergic urticaria: negative ICT
Delayed cold urticaria: negative ICT immediately but positive CSTT after 12 to 48 hours
Localized cold reflex urticaria: negative ICT at site of cube application but positive at sites 5 to 8 cm from site of cube application
Perifollicular urticaria
Localized cold urticaria: positive ICT only in a specific region
Sites of immunization/desensitization
Sites of insect bites
Specific region (etiologic factors unknown)
Familial cold urticaria
Delayed cold urticaria: positive ICT in 9 to 18 hours
Familial cold autoinflammatory syndrome: childhood onset with systemic symptoms on exposure to cold air
Hereditary periodic fever syndromes: negative ICT
Familial Mediterranean fever
Muckle-Wells syndrome (15)
Hyperimmunoglobulinemia D syndrome
Tumor necrosis factor receptor-associated periodic syndrome (also called TRAPS, familial Hibernian fever)
Neonatal onset multisystem inflammatory disease

CSTT, cold stimulation time test; ICT, ice cube test.
 Modified from Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;24:259–286, and Wanderer et al (5). Used with permission.

applied for 15 seconds (approximately the time taken drinking water from the fountain). The 15-second ICT performed on exposed skin of the neck and typically covered skin of the forearm and abdomen were negative also. After more than 2 years, the patient continues to experience cold-induced localized urticaria only on her face. This localization persists even after swimming in cool water. Because the mean age at onset for PACU is 18 to 26 years (6), it may be prudent to observe younger patients with localized urticaria closely for possible progression to systemic manifestations, such as anaphylaxis. If such progression occurred, injectable epinephrine therapy would be appropriate.

It seems unlikely that a systemic humoral factor has a primary role in localized cold urticaria. Investigators have proposed that a regional abnormality of nervous stimulation, such as that in cold reflex urticaria (7), may be involved in localized cold urticaria. In contrast to our

TABLE 2. *Testing for Physical Urticaria*

Cold urticaria
Ice cube test (ICT): Ice cube is placed in plastic bag (or ice slurry is placed in cylinder) and applied to skin (usually forearm) for 20 minutes. Negative result is no urticaria after skin rewarms to normal temperature. Testing in patient with localized case should involve the affected site identified in the patient's history and, if necessary, noninvolved sites.
Cold-dependent dermatographism: After cooling because of ICT, skin is stroked on cooled and noncooled sites. Positive test result is dermatographism of cooled site but not of noncooled sites.
Localized cold urticaria: Positive ICT only in affected site.
Localized cold reflex urticaria: Negative result at ICT application site but hives at 5 to 8 cm from application site.
Cold-induced cholinergic urticaria: Negative ICT result but hives
after exercising in cold environment (4–24°C).
Cold stimulation time test (CSTT): Application of ICT at various intervals (0.5, 1, 2, 5, 10, and 20 minutes) with observation of site for reaction after skin warms to normal temperature. This test is useful for gauging effectiveness of treatments. Application site is observed for 2 days to identify delayed reactions.
Delayed cold urticaria: Application site is observed for 2 days to identify delayed reactions.
Immersion test: Forearm is submerged for 5 to 15 minutes in water at 0 to 8°C. Note: This test can produce shock in patients with generalized cases that include angioedema and should be avoided in these patients.
Heat urticaria
Glass tube test: Glass tube containing water heated to 42 to 45°C is applied to skin for 10 to 20 minutes. Positive result is hives after skin temperature returns to normal.
Exercise test: Exercise is performed to induce sweating and is continued for 5 to 15 minutes. Positive result is small cholinergic hives after cooling.
Pressure test: 6 to 8 kg weight or shoulder band is applied for 15 minutes and site is observed for 20 minutes.

Data from Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;24:259–286; Neittaanmaki (4); and Illig L. Physical urticaria: its diagnosis and treatment. *Curr Probl Dermatol* 1973;5:79–116.

case, wheals in localized cold reflex urticaria characteristically involve the nervous reflex arches surrounding the area of the ICT, rather than the point of contact (7,8). Thus, a chemosensitive nervous stimulus affecting the regional vascular beds (9) may better explain the phenomenon of localized cold urticaria. The findings of marked mast cell degranulation (10) and a documented increase in local histamine at the site of the wheal provide further support for the conclusion that cold urticaria and localized cold urticaria (11,12) involve histamine and, potentially, an aberrant neural response, thus offering a mechanism to help explain the response to antihistamines and cromolyn in cold urticaria cases.

It is curious that rosacea states, carcinoid flush, and flushes associated with medullary thyroid carcinoma seem to involve the head and neck, as well as the upper

chest. An innate sensitivity to thermal and biochemical changes in the head and neck vascular beds may explain why our case and the three cases of localized urticaria all involved the head and neck region.

New mechanisms underlying the histamine inflammatory response itself have come to light only recently. Current investigations suggest that specific to cutaneous neurogenic inflammation, neuropeptides such as substance P and calcitonin gene-related peptide are synthesized within keratinocytes and dermal endothelial cells. Activation of proteinase-activated receptors, which are expressed on sensory neurons, dermal cells (13), and mast cells (14) induces the release of neuropeptides, substance P, and calcitonin gene-related peptide. The result is the release of histamine and other inflammatory mediators. To prevent this release in operative settings, care to avoid placement of postoperative ice packs on areas of localized, as well as generalized, cases of cold urticaria is advised (6).

CONCLUSION

We present this case as another example of the varied and unusual presentation of acquired localized cold urticaria. It is a reminder to test at the sites in which the urticarial reaction occurs, because testing at distant sites may result in negative findings that mislead the physician. Although the mechanisms of cold urticaria remain obscure, localized neurosensory response and local neuropeptide substances offer a potential explanation for this curious process.

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