



## Cold-induced urticaria

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Cold-induced urticaria is a form of physical urticaria that develops on cold exposure in susceptible individuals. The majority of cases have an unknown etiology (primary or idiopathic). In rare forms, it is associated with various disease entities (secondary). The workup of a patient includes a history and physical examination, cold challenge, and a battery of laboratory tests. The management of such patients includes precaution and avoidance measures as well as treatment with antihistamines. Life-threatening symptoms necessitate carrying a self-administered injectable epinephrine.

(Key words: urticaria, physical urticaria, cold-induced urticaria)

It has been more than a century since the original description of cold-induced urticaria, but information on its presentation, disease associations, and management is still expanding.<sup>1</sup> Cold-induced urticaria is a syndrome that, as the name implies, develops on cold exposure. Such exposure varies from local contact such as holding a cold object, immersing body parts in cold or ice water or ice, to systemic exposure including wind, and walking or swimming in cold environments. Some symptoms may develop on local exposure and others by only total-body exposure to cold environments. Although the syndrome has been termed “cold urticaria” or “cold-induced urticaria,” hives are only one of the manifestations of the syndrome. In some forms of cold-induced urticaria, the urticarial compo-

nent does not develop.<sup>2</sup> It is noteworthy that not all symptoms associated with cold-induced urticaria may exist in the same individual (*Figure 1*).

### Clinical diagnosis

A focused history helps to arrive at the clinical diagnosis of cold-induced urticaria. *Figure 2* summarizes suggested questions to ask during the initial assessment. A common diagnostic test is called the “ice-cube test.” One simply places an ice cube on the patient’s forearm (volar aspect) for 5 minutes. On removal of the ice cube, erythema is noted and pruritus develops between 2 to 4 minutes and a hive within 10 minutes (positive test).<sup>3</sup>

Other cold-exposure tests include an immersion test, in which the patient’s hand is placed in ice water (0°C) for 4 minutes.<sup>4</sup> Alternatively, the patient is taken to a cold room (4°C) and remains there for 10 to 30 minutes. *Figure 3* summarizes the workup of patients with suspected cold-induced urticaria.

Not all forms of cold-induced urticaria will respond to these simple tests. Also, caution is necessary because systemic symptoms may occur when

large portions of the body are tested. An example is that after the immersion test, the blood histamine level increases, and some patients may have wheezing develop or have a drop in blood pressure.

### Classification

Cold-induced urticaria can be classified based on:

- etiology,
- response time of symptoms,
- extent of the symptoms,
- type of presenting symptoms,
- simplicity of presentation (*Figure 4*).

Cold-induced urticaria is either acquired or familial. The acquired form is categorized as primary (idiopathic), etiology unknown, or secondary. Patients with primary (idiopathic) and secondary cold-induced urticaria have an immediate positive response to the cold stimulation test, but secondary cold-induced urticaria is associated with other entities such as serum proteins (cryoglobulin, cryofibrinogen, cold agglutinin, hemolysin),<sup>5</sup> bee stings,<sup>6</sup> infectious mononucleosis,<sup>7</sup> measles,<sup>8</sup> the human immunodeficiency virus,<sup>9</sup> vasculitis,<sup>10</sup> hypothyroidism,<sup>11,12</sup> and medications such as oral birth control pills<sup>13</sup> and antifungal therapy.<sup>14</sup> Despite multiple causes, the majority of cases are idiopathic or primary in etiology.

The familial form of cold-induced urticaria is a rare entity. It is an autosomal-dominant trait disorder. Onset occurs in infancy. The response to the ice-cube test is usually negative, but patients have a positive response when challenged in a cold room for 0.5 hour to 6 hours. Systemic symptoms include fever, chills, arthralgia, and headaches. Skin lesions include erythematous, papular, and burning ones but no urticaria.<sup>2</sup>

Another way of classifying cold-induced urticaria is based on time of appearance of the skin lesion: immediate, in which urticaria develops after a few minutes after exposure to cold; delayed, in which urticaria develops in as long as 48 hours postexposure.<sup>11</sup> Most episodes of cold-induced urticaria are immediate, and the response to the ice-cube test will be positive within a few

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## Checklist

### ■ Localized symptoms

- Burning sensation
- Cold-dependent dermatographism
- Erythema
- Pruritus
- Urticaria or angioedema (or both)

### ■ Systemic symptoms

- Angioedema
- Arthralgias
- Anaphylaxis
- Abdominal pain
- Burning
- Chills
- Dyspnea
- Death
- Fever
- Fatigue
- Faintness or shock
- Headaches
- Hypotension
- Nausea
- Tachycardia
- Urticaria, generalized
- Vertigo
- Wheezing

**Figure 1.** Localized and systemic symptoms with cold-induced urticaria.

minutes after removal of the ice cube from the arm.

The symptoms of cold-induced urticaria are either localized, in which developing symptoms (such as urticaria, burning, erythema, pruritus) are a result of exposure of body parts—usually the hands or face—to cold, or systemic, in which developing symptoms are as a result of total-body exposure to cold (such as cold wind, swimming in cold water, or cold-room challenge) (Figure 4). The symptoms occurring postexposure to cold are either typical, localized, as previously described, or atypical such as localized cold-reflex urticaria (lesions occur in locations other than the exposed site)<sup>15</sup>; cold-induced cholinergic urticaria (lesions are similar to cholinergic urticaria)<sup>16</sup>; or cold-dependent dermatographism (cold skin is needed for



## Checklist

- How do the symptoms develop?
  - by holding a cold object?
  - application of an ice bag?
  - immersing hands or feet in cold or icy water?
  - ingesting cold/icy food?
  - swimming in cold water?
  - walking into cold rooms?
  - walking or running in cold weather?
  - staying in cold weather?
- What are the symptoms?
  - skin involvement only?
  - systemic involvement?
  - both skin and systemic involvement?
- How soon after exposure do symptoms occur?
- Are the symptoms activity related?
- Are there any other situations that produce symptoms similar to cold exposure, such as heat exposure, vibration, pressure?
- Are you healthy otherwise? What other illness(es) occurred before the onset of the cold-induced symptoms?
- How long have you had the symptoms?
- Thinking back, did the symptoms start after an illness?
- Have you started taking a new medication lately? If so, is there any temporal association between the onset of taking that medication and the cold-induced symptoms?

**Figure 2.** Suggested questions during initial assessment for cold urticaria.

dermatographism to develop).<sup>5,17</sup>

Cold-induced urticaria may present as a single entity or in combination with other types of urticaria. In one study of 220 patients with cold-induced urticaria,<sup>11</sup> in addition to cold-induced urticaria, 2 patients (0.9%) had heat-induced urticaria, 4 (1.8%) had chronic urticaria, 2 (0.9%) had cholinergic and dermatographism, 15 (6.8%) had cholinergic urticaria, 2 (0.9%) had dermatographism and



## Checklist

- Complete history and physical examination
- Cold challenge test, such as ice-cube test or total-body exposure to cold
- Complete blood cell count with platelet and differential cell counts
- Erythrocyte sedimentation rate
- Chemistry profile (liver function and renal function tests)
- Rheumatoid factor
- Serum immunoglobulin levels
- Complement C3, C4, and total hemolytic complement (CH50) levels
- Antinuclear antibody level
- Serum protein electrophoresis
- Serum cryoglobulin level
- Serum cryoprecipitin level
- Serum fibrinogen level
- Cold agglutinin level

**Figure 3.** Suggested workup for assessment of cold-induced urticaria. First five tests listed should be done in all patients. The remaining tests listed should be done if history, physical examination, initial laboratory assessment, or clinical suspicion suggests a secondary cause.

chronic urticaria, and 42 (19.1%) had dermatographism.

### Pathophysiology

As a result of cold challenge in patients with cold-induced urticaria, multiple mediators have been found to be elevated including: histamine,<sup>4</sup> neutrophil chemotactic activity,<sup>18</sup> tumor necrosis factor- $\alpha$ ,<sup>19</sup> prostaglandin D<sub>2</sub>,<sup>20</sup> platelet-activating factor-like lipid,<sup>21</sup> eosinophilic chemotactic factors,<sup>22</sup> and platelet factor 4.<sup>23</sup>

Involvement of various factors and mediators in patients with cold-induced urticaria implies that perhaps the etiology of cold-induced urticaria is multifactorial and the pathophysiology is complex. The exact interaction of the factors and mediators released on cold challenge in such patients is still not quite clear.

## Treatment

The classic treatment for cold-induced urticaria is cyproheptadine hydrochloride; however, it is suspected that all antihistamines may be effective. The data supporting the use of doxepin hydrochloride include a study by Neittaanmaki,<sup>24</sup> who conducted two randomized, double-blind trials to compare various antihistamines in the treatment of idiopathic cold-induced urticaria. In the first trial, doxepin was compared with cinnarizine and placebo. The majority of patients preferred doxepin over cinnarizine. In the second trial, doxepin was compared with cyproheptadine, hydroxyzine, and placebo. Although there was statistically significant suppression of wheals in ice-cube tests, no significant differences in such effect were noted among drugs tested. The majority of patients (6 of 11) reported doxepin as the most effective treatment. Starting at 10 mg/d at bedtime is probably necessary in most patients to avoid somnolence during the day. The dose of doxepin can be gradually increased to effect.

Cetirizine hydrochloride has also been found to be effective. One study reported the effect of cetirizine on 12 patients with cold-induced urticaria.<sup>25</sup> Patients ranged in age from 18 to 72 years. They were tested with ice cube first and again 4 hours after administration of cetirizine, 10 mg. In 5 patients, urticaria disappeared, and in the remaining 7 patients, urticaria decreased.

Other comparative studies have documented the effect of cyproheptadine versus chlorpheniramine in patients with primary acquired cold-induced urticaria.<sup>26</sup> The authors designed a double-blind comparative study in which eight patients (age range 7 to 60 years) with primary acquired cold-induced urticaria were randomly assigned to receive either drugs or placebo in a sequence of 7-day periods each with 7-day rest intervals. Results of the study indicated that the minimum time of cold stimulation to appearance of urticaria was increased after cyproheptadine treatment when compared with chlorpheniramine or placebo.



## Checklist

- **Based on etiology**
  - Acquired
    - primary (idiopathic)
    - secondary
  - Familial
- **Based on response time of symptoms**
  - Immediate
  - Delayed
- **Based on extent of the symptoms**
  - Localized
  - Systemic
- **Based on type of presenting symptoms**
  - Typical
  - Atypical
- **Based on simplicity of presentations**
  - Simple—presence of one type of cold-induced urticaria
  - Compound—more than one type of cold-induced urticaria

Figure 4. Various classifications of cold-induced urticaria.

Whatever antihistamine is prescribed, it is important to also prescribe an injectable epinephrine such as EpiPen. Symptoms of wheezing and syncope have been described, and epinephrine may be needed in severe cases. Systemic reaction is particularly important when swimming, because it may lead to drowning. Besides the use of medication, certain precautionary measures need to be followed, including avoiding cold environments such as cold weather, ice, snow, and water. If the cold exposure is necessary, then the time of exposure should be limited to avoid a life-threatening situation. Appropriate dress in winter should provide adequate protection in the majority of cases. Swimming should be avoided, and if swimming is unavoidable, a partner should always be present and know how to use the available epinephrine or anaphylaxis

treatment kit (Ana-Kit) so as to administer emergent therapy if needed.

## Comment

Cold-induced urticaria is an entity in which typical symptoms of urticaria, erythema, and pruritus develop in the sites of cold exposure. At times, manifestations of cold exposures are atypical. Cold-induced urticaria has equal incidence in both sexes and can occur at any age. The etiology of cold-induced urticaria in the majority of those affected is unknown (idiopathic). At times, disease or other factors are associated with cold-induced urticaria; then, cold-induced urticaria is classified as secondary. Precaution, avoidance of prolonged cold exposure, and antihistamines are the mainstay of management of cold-induced urticaria, with epinephrine as a backup.

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