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Modern Approaches to the Diagnosis and Treatment of Cold Contact Urticaria

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Abstract Cold contact urticaria (CCU) is a common subtype of physical urticaria characterized by itchy wheals and/or angioedema due to skin mast cell activation and the release of proinflammatory mediators after cold exposure. The underlying causes are largely unknown. When CCU is suspected, cold stimulation tests and threshold testing should be done to confirm the diagnosis and to determine the severity and course of CCU, respectively. Avoidance of critical cold exposure should be recommended but is often impossible, especially for severely affected patients with high temperature and low exposure time thresholds. Symptomatic treatment of choice is the use of modern, nonsedating antihistamines. Patients should be informed that complete protection from CCU symptom development may require increased doses of antihistamines. Standardizing cold provocation tests and further characterization of the natural course of CCU and its variants may lead to a better understanding of the disease-driving mechanisms.

Keywords Cold urticaria · Physical urticaria · Cold stimulation test · Threshold test · Antihistamine · Treatment

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Introduction

Clinical Picture and Epidemiology

Among all physical urticarias, cold contact urticaria (CCU) represents the second most common subtype after symptomatic dermographism [1]. Also referred to as *acquired cold urticaria* or just *cold urticaria*, the term *cold contact urticaria* is used in accordance with the recent international position papers on the classification and diagnosis of urticarias [2, 3]. CCU is characterized by the development of wheals and/or angioedema due to the release of histamine and other proinflammatory mast cell mediators following exposure of the skin to cold. Typically, symptoms occur within minutes after cold contact, including exposure to cold air, liquids, or objects, and persist for up to 2 h. Wheals usually appear only at skin sites exposed to the cold stimulus. However, extensive cold contact of large skin areas (eg, swimming in cold water) may lead to systemic reactions such as generalized urticaria, dyspnea, tachycardia, hypotension, and loss of consciousness [4, 5]. Several deaths in CCU have been reported due to anaphylaxis while swimming in cold water. The percentage of CCU patients who experience at least one systemic reaction after extensive cold contact lies between 35% and 72% [4–7]. A history of oropharyngeal angioedema associated with the consumption of cold beverages or food seems to be correlated with high disease severity [8]. The onset of CCU symptoms may occur at any age but shows a peak in young adults and a weak predominance in women [4, 5, 9]. A positive correlation between early onset of CCU and disease severity in terms of cold-induced systemic symptoms also could be observed [7]. The mean duration of symptoms ranges between 4.8 and 7.9 years [4, 5, 9]. The annual incidence of CCU was estimated to be 0.05% [9].

Pathogenesis and Etiology

The symptoms of CCU are caused by the activation of mast cells. Following cold provocation, cutaneous mast cells in CCU patients show signs of degranulation [10], and serum levels of histamine and other mast cell mediators, including tumor necrosis factor-α, prostaglandin D_2, a neutrophil chemotactic factor, and platelet-activating factor-like lipid, were found to be increased [11–15]. Furthermore, cold challenge of skin biopsy specimens reportedly yields histamine release without any intact nerves [16]. However, the activation of skin nerves in vivo may augment the pruritus, burning, and erythema seen. The resulting vasodilatation and extravasation of skin vessels cause wheals and angioedema. As of yet, the mechanisms and signals for cold-dependent mast cell activation have not been identified; thus, the etiology of CCU remains largely unclear. Passive transfer studies revealed a subpopulation of patients in whom IgE antibody was shown to mediate cold sensitivity; nevertheless, the mechanism by which this occurs is unknown.

Although no underlying causes are detectable in most CCU patients, an association of CCU with cryoglobulinemia and hematologic disorders has been described in small subsets of patients [17]. Also, a link between CCU and various viral, parasitic, or bacterial infections could be observed [18–20]. In addition, individual patients exhibit CCU onset shortly after insect and jellyfish stings [21, 22] or the intake of drugs [23]. However, CCU secondary to other conditions is rare compared with the number of idiopathic cases.

Diagnostic Procedures

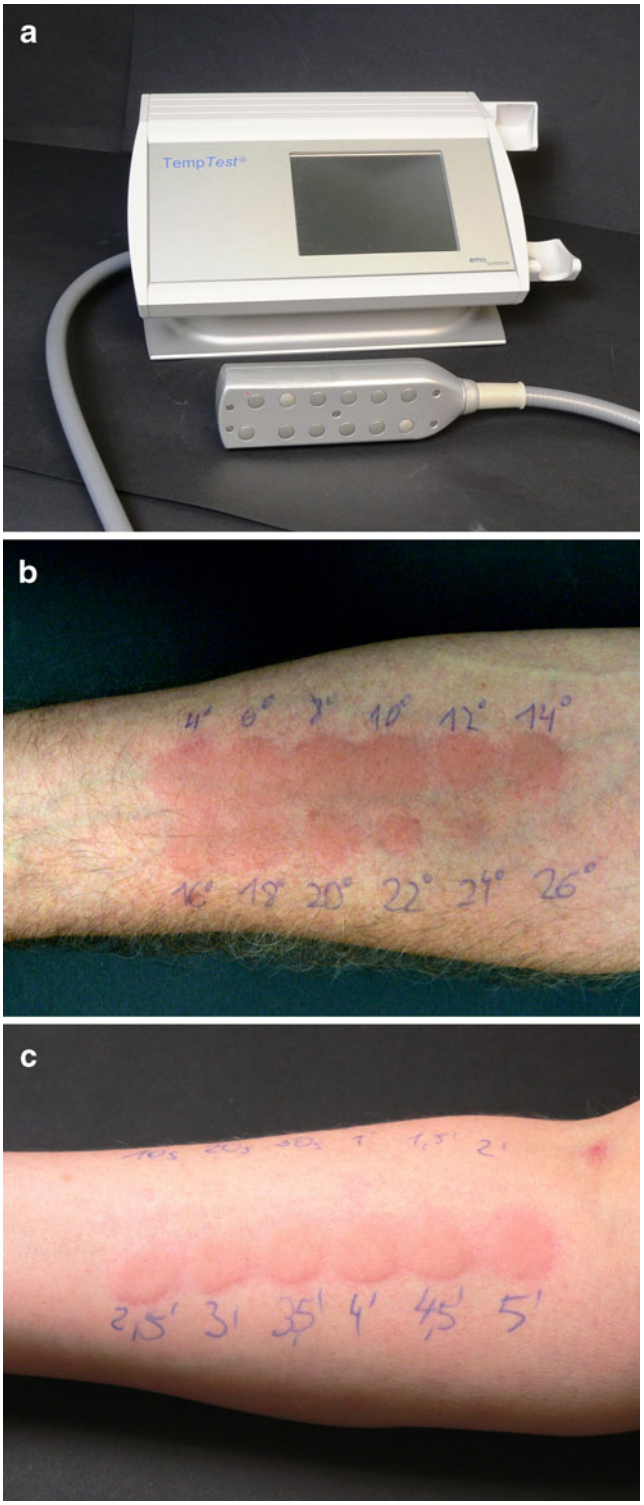
Provocation Testing

CCU is verified by a positive cold stimulation test (CST) (ie, the development of urticarial skin lesions at sites of cold challenge) [24, 25]. CSTs are done by using ice cubes, cool packs, cold water baths, or TempTest (Emo Systems, Berlin, Germany), a Peltier element-based cold provocation device (Fig. 1). The simplest method is to place a melting ice cube in a thin plastic bag on the volar forearm for 5 min. The ice cube should be melting to avoid cold damage of the skin and contained in a thin plastic bag to prevent confusion with rare aquagenic urticaria if the test is positive. The test response is assessed 10 min after removing the ice cube. It is considered positive and the diagnosis of CCU is confirmed if the test site shows a palpable and clearly visible wheal-and-flare-type skin reaction [2]. If there is no wheal reaction (e.g. erythema or pruritus/burning only), the test is considered negative. The use of cool packs and cold water baths for CSTs requires caution and is not recommended for first-line screening tests because these methods may induce systemic reactions [15]. To assess disease severity and response to treatment in CCU more precisely, patients should be evaluated for individual temperature and/or stimulation time thresholds [25, 26•]. Individual threshold testing determines the highest temperature and/or the shortest stimulation time sufficient for inducing a wheal-and-flare reaction. Cold stimulation time tests to characterize the activity, prognosis, and course of CCU were already described more than 20 years ago. Wanderer et al. [4] placed ice-filled plastic bags on the forearm of CCU patients and assessed the minimum exposure time required to induce whealing. A negative correlation between the severity of CCU symptoms and the duration of stimulation times was reported (ie, temperature thresholds of ≤ 3 min were found to be associated with higher disease activity compared with temperature thresholds of > 3 min) [4]. Recently, a Peltier element-based electronic provocation device (TempTest) was developed (Fig. 1a). The simultaneous application of 12 different temperatures, from 4.0°C to 42.0°C, allows for a quick, reproducible, and standardized evaluation of critical temperature thresholds (Fig. 1b) and time thresholds (cold stimulation time tests) (Fig. 1c) [25]. Evaluation of 30 patients with a history of cold-induced urticarial symptoms showed a comparable number of positive responses to ice cube (83%) and TempTest (92%) testing [25]. It could be demonstrated that temperature thresholds in CCU patients reflect their disease severity. Also, changes in critical temperature thresholds corresponded to changes in CCU activity [26•]. Threshold testing may not only be used for monitoring disease activity in CCU but may also help patients to better cope with their disease and to avoid dangerous situations in daily life.

The results of provocation tests in general can be influenced by certain drugs (especially antihistamines, high-dose oral or topical steroids, and immunosuppressive agents), which should be withdrawn before testing if possible. Furthermore, provocation tests should not be performed in skin areas that have been affected by urticaria during the previous 24 h, because skin sites exhibit a refractory period after urticarial reactions.

Laboratory Work-Up

Laboratory investigations in patients diagnosed with CCU should be restricted to cases in which the patient's history strongly suggests the existence of an underlying disease. If indicated, laboratory work-up may include a differential blood count, inflammation markers such as C-reactive



◀**Fig. 1 a**, Peltier element-based electronic provocation device (TempTest; Emo Systems, Berlin, Germany) with 12 stimulators to confirm cold contact urticaria and to determine individual temperature and exposure time thresholds. **b**, Positive test reaction after critical temperature threshold testing with TempTest on volar forearm. Critical temperature threshold in the test reaction site shown is 22°C. **c**, Positive test reaction after stimulation time threshold testing with TempTest on volar forearm. Critical stimulation time threshold in the test reaction site shown is 2.5 min

protein and erythrocyte sedimentation rate, cryoglobulins, antinuclear antibodies, and bacterial or viral serologies. However, in most patients, the etiology of CCU is idiopathic, and even comprehensive testing does not reveal underlying causes.

Differential Diagnosis

Atypical Cold Urticarias

Patients with a history suggesting cold-induced urticaria but without a response to conventional ice cube and/or TempTest testing should be tested carefully using larger provocation areas (eg, by using cool packs or cold-water baths). If additional CSTs are also negative, atypical cold urticaria may be suspected. Atypical cold urticarias are very rare entities that are characterized by negative (or atypical) cold provocation tests result. In single case reports, systemic cold urticaria, cold-dependent dermographism, cold-induced cholinergic urticaria, delayed cold urticaria, and localized cold reflex urticaria have been described (Table 1) [24, 27–31]. However, it is not clear whether these are independent entities or whether they originate from conventional CCU. There have been reports of patients in whom CST responses converted from positive to negative results over the years, although these patients continued to exhibit urticaria due to cold air [32].

Familial Cold Urticarias

In CST-negative patients with a personal and family history of cold-induced whealing, familial forms of cold urticaria should be considered. Three very rare hereditary types have been recognized thus far (Table 2).

Familial cold autoinflammatory syndrome (FCAS) is an autosomal-dominant inherited disease that belongs to the cryopyrin-associated periodic syndromes (CAPS). All CAPS entities are caused by a mutation in the cryopyrin gene [33]. FCAS is characterized by urticaria-like skin rashes that develop 1 to 2 h after generalized cold exposure. Associated symptoms are fever, chills, arthralgia, headache, and conjunctivitis [34]. Amyloidosis, a common feature of other CAPS, is rarely seen in FCAS. Usually, cold-induced rashes start immediately after birth or within the first 6 months and persist lifelong. Episodes last for an average of 12 h and then subside. However, most patients report some baseline daily symptoms even in the absence of cold exposure [24].

Familial delayed cold urticaria and the newly described familial atypical cold urticaria also show an autosomal-

Table 1 Atypical cold urticaria (immediate cold stimulation test always negative)

Disorder	Clinical characteristics
Systemic cold urticaria	Cold, humid air induces wheeling, which can be localized or generalized
Cold-dependent dermographism	Dermographic wheals are limited to stroking of precooled skin
Cold-induced cholinergic urticaria	Generalized wheeling due to exercise in cold environment
Delayed cold urticaria	Localized wheeling 12–48 h after cold exposure
Localized cold reflex	Wheeling response occurs near the site but not directly at the site of cold provocation

dominant pattern of inheritance. In familial delayed cold urticaria, the immediate CST is negative, and urticarial symptoms develop no earlier than 9 to 18 h after cold exposure. The wheals may resolve in hyperpigmented macules [35]. Familial atypical urticaria presents with lifelong cold-induced urticaria, negative CSTs, and without further inflammatory symptoms such as fever or joint pain, as seen in CAPS [36]. The mutation(s) responsible for the clinical symptoms seen in these two inherited cold-associated urticaria forms remain(s) to be identified.

Management

Prevention

As a first step, patients with CCU should be urged to avoid cold exposure to prevent urticarial symptoms as much as possible. Patients should be advised not to engage in aquatic activities and to abstain from consuming ice-cold food and beverages, which bear the risk of oropharyngeal edema. The knowledge of temperature and/or time thresholds can help patients to better recognize and control cold exposure in their daily lives. Nevertheless, patients with high temperature thresholds often experience considerable quality-of-life impairment, as avoidance of cold exposure is difficult and often insufficient.

Symptomatic Treatment

The symptomatic treatment of choice in CCU is the use of nonsedating H1 antihistamines [37]. Various antihistamines have been reported to be successful in the management of CCU over the past decades. A beneficial therapeutic response in CCU was already shown with first-generation antihistamines such as cyproheptadine and doxepin [38, 39]. However, these agents are no longer recommended as first-line treatment due to considerable anticholinergic and sedating side effects [37, 40]. Other nonsedating H1 antihistamines including cetirizine, mizolastine, ebastine, desloratadine, and rupatadine, have been demonstrated to be effective in protecting against or reducing the clinical symptoms of CCU [41–43, 44••, 45]. Depending on the disease severity, antihistamines are used on demand only (usually in patients with a low temperature threshold and mild symptoms) or as prophylactic treatment (in patients with a high temperature threshold and/or experience of systemic reactions after cold exposure). Nevertheless, many patients do not respond satisfactorily to standard daily doses of antihistamines. Recent data have shown that updosing of H1 antihistamines is safe and more effective in reducing symptoms in CCU than single-dose treatment. Desloratadine, 20 mg, compared with desloratadine, 5 mg, over 7 days resulted in significantly improved temperature and stimulation time thresholds. In addition, high-dose desloratadine provided complete protection from CCU symptoms in 50% of all patients, compared with only 23% of patients in the 5-mg group [44••]. A similarly good response was observed with combined antihistamine and platelet-activating factor antagonist rupatadine treatment in the reduction of CCU symptoms [46]. As high-dose desloratadine and rupatadine were well-tolerated in both studies, the use of increased doses of H1 antihistamines in CCU patients whose symptoms are insufficiently controlled at standard dosage is supported [37]. In patients with severe CCU who continue to experience symptoms despite

Table 2 Familial cold urticarias

Disorder	Clinical characteristics
Familial cold autoinflammatory syndrome	Urticarial rash develops 1–2 h after cold exposure; associated symptoms include arthralgia, conjunctivitis, fever, chills, headache; mutation in *CIAS1* gene; CST negative
Familial delayed cold urticaria	Urticaria-like skin reaction develops 9–18 h after cold exposure, may resolve with hyperpigmentation
Familial atypical cold urticaria	Immediate wheeling reaction develops after cold exposure; CST negative

CST—cold stimulation test

updosing of H1 antihistamines, the concomitant use of leukotriene antagonists or H2 blockers has been described [47]. In single cases of high disease activity, the successful use of ciclosporin and anti-IgE therapy in CCU has been reported [48, 49]. Very recently, a case of severe CCU was described with complete remission of symptoms after initiation of treatment with the interleukin-1 antagonist anakinra [50••].

Emergency Treatment

CCU patients are at risk of anaphylaxis or oropharyngeal edema. Severely affected patients with a history of anaphylaxis or systemic symptoms, should an emergency kit containing an adrenaline injector, corticosteroid, and antihistamine carry. The use of an adrenaline pen has been demonstrated to be life-saving in severe systemic reactions of CCU [51].

Others

As the underlying causes of CCU are largely unknown, targeted curative therapies are lacking. There are reports of successful antibiotic treatment with penicillin or tetracycline leading to complete disease remission in CCU [9]. However, a benefit has not only been demonstrated in cases of CCU coinciding with infection but also without detectable infection. Thus, it is not known whether antibiotic treatment truly cures an underlying infection or interacts with unknown trigger factors of CCU.

As a topical treatment option, the use of capsaicin, an ingredient of chilli peppers, has been reported. In a small case series, the topical use of capsaicin resulted in the prevention of urticarial symptoms for several days [52]. Nevertheless, it should be noted that 1) capsaicin evokes burning and stinging of the skin and 2) data from controlled trials are lacking.

Tolerance Induction

Cold tolerance induction and its maintenance represent a further possibility to prevent clinical symptoms in CCU patients [53]. To achieve cold desensitization, repeated exposures to cold temperatures (eg, by taking cold baths or showers) are required. Usually, tolerance induction starts with above-threshold temperature exposure of limited skin areas and is gradually intensified with an increase of body surface and decrease of temperature until no more symptoms occur upon whole body exposure to cold water. Due to the risk of severe systemic reactions, patients must be supervised by a physician and need to continue to take daily cold showers to maintain tolerance. However, daily cold exposures are time consuming and bothersome for most patients, and in our experience, very few patients manage to adhere to this therapy regimen over a longer period of time. In a retrospective study, all participating CCU patients discontinued cold water treatment after weeks or months because of side effects or lack of motivation, and all of them experienced complete recurrence of cold-induced symptoms [54].

Conclusions

CCU is a disease that can be easily diagnosed using cold provocation testing. Clinical manifestations can range from mild, localized whealing to life-threatening anaphylactic shock reactions. Rare atypical cold urticaria forms or hereditary cold-associated syndromes are distinguished from CCU by negative CSTs and a positive family history. Owing to the recent improvement in diagnostics, patients can now be assessed by standardized techniques for their individual temperature and stimulation time thresholds. The underlying causes of CCU remain largely unknown.

Case reports regarding beneficial responses to anti-IgE and anti-interleukin-1 demonstrate that there are additional treatment options on the horizon apart from antihistamines [49, 50••]. Anti-interleukin-1 therapy, for example, is known to be highly effective in all CAPS entities, including FCAS [55]. Interleukin-1β is activated by the cryopyrin-containing inflammasome and plays an essential pathogenic role in CAPS [56]. Thus, the response to anti-interleukin-1 in CCU without evidence of a mutation in the cryopyrin gene may be of particular interest to gain a better understanding of the underlying pathomechanisms in CCU.

Considering the diverse forms of CST-negative atypical cold urticarias, very few data are available about incidence, course, and treatment response. Furthermore, it is often not clear whether these are independent entities or variations of formerly CST-positive CCU. To understand the disease-driving mechanisms, it is therefore also important to better characterize and follow up all cold-induced urticaria forms and to further standardize and harmonize cold provocation test protocols.

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- •• Of major importance

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