

Case Report

COLD URTICARIA IN A CHILD: A CASE REPORT

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SUMMARY

Over a one-month period, a 2½-year-old child presented with a recurrent history of an itchy rash involving the limbs, feet, lip and tongue swelling ten minutes after eating an ice lolly. A diagnosis of cold urticaria was made, responsive to antihistamines. She now tolerates cold foods.

Keywords: cold urticaria, angioedema, antihistamines, temp test, ice-cube test

CASE

A 2½-year-old child presented at an outpatient clinic of a tertiary hospital in Cape Town, South Africa, with a history of an itchy rash over the feet that spread gradually to involve the knees and hands. Initial treatment included chlorphenamine, a non-steroidal anti-inflammatory syrup and a topical corticosteroid cream. She was discharged from the clinic. A few hours later, she ate an ice lolly that resulted in almost immediate lip and tongue swelling. She was rushed to hospital, where chlorphenamine was given again. Additional treatment included adrenaline nebulisation, oral prednisone and oxygen delivered via a face mask. No intramuscular adrenaline was given. However, her parents mentioned a five-day history of coughing and rhinorrhoea, without any fever.

On examination, she was alert, had normal vital signs, but appeared miserable. Her lips appeared visibly swollen. No features of anaphylaxis were present. The left foot had a single urticarial lesion and was mildly swollen. All other organ systems were normal.

The initial diagnosis was urticaria with angioedema most likely secondary to a viral upper respiratory-tract infection. She was admitted to hospital for observation. The lesions disappeared within 24 hours. She remained well and was discharged home.

Two weeks later, a third episode of itchy bumps on the arms and legs, accompanied by swollen lips, was reported after eating an ice lolly (see Figures 1 and 3). She had also eaten a corn snack during the same period. Symptoms appeared within ten minutes after ingestion and seemed less severe than the previous episodes, with bumps lasting only 2–3 hours during this episode. No fever and no joint or muscle pains were reported. At that stage, the differential diagnoses included cold urticaria, food-preserved hypersensitivity, food-colourant hypersensitivity or a viral infection. She was admitted to hospital again and given antihistamines. She was discharged the following day. A follow-up date for further testing was set. No regular antihistamine was prescribed. During follow-up, the following tests were performed

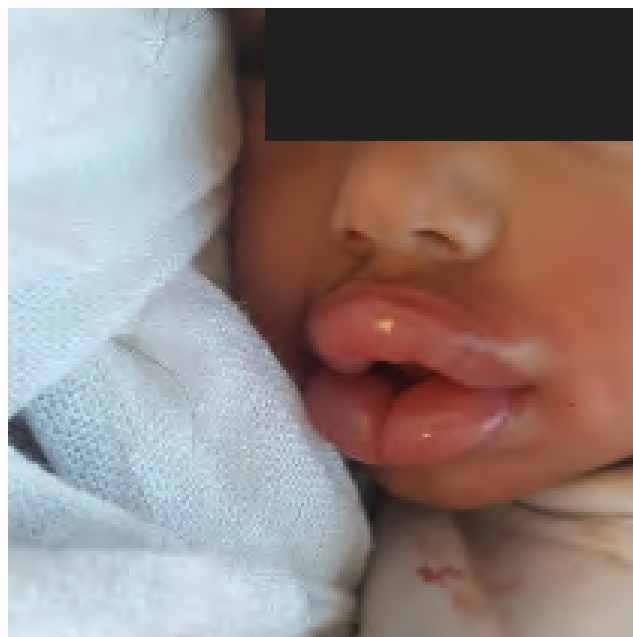


Figure 1: Angioedema after ingesting an ice lolly

(the results of these tests are given in brackets):

- ice cube test (positive)
- full blood count and differential count (normal)
- erythrocyte sedimentation rate (normal)
- complement C4 levels (normal)
- radioallergosorbent tests (RAST) to almonds, cashew nuts, hazel nuts, pecan nuts and sesame were all negative
- a Cellular Antigen Stimulation Test (CAST) to monosodium glutamate, tartrazine, benzoates, food colourants, nitrates and guar gum, a thickening agent, were negative.

Of note, however, is that the CAST to sulphites was positive.

She was discharged from hospital with advice to avoid cold

foods, cold drinks, cold surfaces and foods containing sulphites. Advice was given to always test the temperature of water and to observe the appearance of skin urticaria or swelling before dipping her feet into it. After discharge, regular oral fexofenadine twice a day provided good symptom control. Several months later, she tolerated ice cream, ice lollies and fridge water, and was even able to swim in the ocean, without any skin or systemic reactions.

DISCUSSION

Cold urticaria is a sub-set of a wide heterogenous group of disorders characterised by the rapid appearance of wheals and/or angioedema.¹ Cold urticaria, also known as acquired cold urticaria (ACU), is a condition triggered by a cold stimulus such as cold water, air, wind, food or drinks. This results in the release of histamine and other mast-cell proinflammatory mediators, with subsequent wheal formation either with or without angioedema.²

Cold urticaria affects mostly young adults and more frequently young females.^{2,3} It can either be primary (idiopathic) or secondary (acquired). The majority of cases are primary, with patients having no identifiable disease.⁴ In secondary cold urticaria, patients have a suspected underlying condition or disease. Some potential underlying conditions include infections such as HIV, autoimmune diseases, lymphoproliferative diseases and cryoglobulinaemia with or without malignancy.^{4,5} Cold urticarias can also be atypical, with wheals being triggered only by a unique combination of environmental conditions rather than a single environmental factor. The atypical cold urticarias tend to show more severe symptoms with a negative cold stimulation test.⁶ Some atypical cold urticarias can be familial, exhibiting an autosomal dominant transmission pattern, presenting early in childhood and enduring a lifetime.⁷

Diagnosis can be difficult. Atypical cold urticarias can be sub-classified into localised cold urticaria, localised cold reflex urticaria, delayed cold urticaria, cold-induced cholinergic urticaria, cold-dependent dermatographism and systemic reactions associated with cold urticaria. The severity of symptoms varies and can be classified as:

- Grade I: Localised cutaneous symptoms
- Grade II: Diffuse cutaneous symptoms
- Grade III: Anaphylaxis⁶



Figure 2: Wheal formation on the left forearm after an ice-cube test

TABLE I: CLINICAL FEATURES OF COLD URTICARIA

SYSTEM	CLINICAL FEATURES
Constitutional symptoms	Fever, fatigue
Skin and mucus membranes	Wheals, angioedema of the lips, tongue, pharynx
Respiratory system	Nasal congestion, dyspnoea
Gastrointestinal system	Nausea, abdominal pains, diarrhoea
Cardiovascular system	Tachycardia, hypotension, shock
Reproductive system	Uterine contractions
Central nervous system	Headache, vertigo, disorientation, fainting, loss of consciousness

PATHOGENESIS

The underlying pathophysiological mechanism of cold urticaria remains largely unknown. Some mechanisms under consideration include autoallergy, autoimmunity and neuronal pathways. IgE-mediated autoimmunity has been proposed with the production of autoantigens and during the sensitisation phase, IgE antibodies upon cold exposure. On re-exposure, mast-cell degranulation causes wheal formation and angioedema. By using autologous skin testing and basophil histamine release assays, Type-IIb autoimmunity was demonstrated in a few reported patients with cold urticaria.⁵

The role of nerve fibres in the pathogenesis of cold urticaria was demonstrated in a study which used capsaicin pre-treatment that resulted in delayed wheal formation for 4–7 days. This is in view of capsaicin's role in impairing chemo-sensitive nerve endings.⁸

CLINICAL FEATURES

The clinical features are summarised in the Table I.

COMORBIDITIES

Cold urticaria may be associated with other chronic inducible urticarias such as dermatographism, cholinergic urticaria and heat urticaria.⁸ A US-based study assessing acquired cold urticaria over a 22-year period found the majority of patients to have a co-existing history of other atopic diseases.³ A study assessing the presence of inducible urticaria in patients with chronic spontaneous urticaria (CSU) showed that 13.4% of the patients had concurrent cold urticaria.⁹

DIAGNOSIS OF COLD URTICARIA

The diagnosis of cold urticaria includes a thorough history and provocation testing.^{7,10} Enquiring about the age of onset of the disease, the frequency and duration of wheals, diurnal variation, shape, size and distribution of wheals, associated angioedema, associated subjective symptoms of lesions (itching and pain), family history of atopy/urticaria, current allergies, infections or internal diseases, induction by physical stimuli, use of drugs (eg NSAIDs), immunisations, occurrence in relation to weekends, holidays and foreign travel, stress and quality of life impairment related to urticaria, are important questions during history-taking.



Figure 3: Wheal formation on lower limb after consuming an ice lolly

The provocation tests can be done by using an ice cube or by performing the Temp Test.⁵ During ice-cube testing, an ice cube, placed in a plastic bag or a glove, is placed on the patient's forearm (avoid an area that had urticaria 24 hours prior to testing) for 3–5 minutes. A response is then measured ten minutes later¹¹ (see Figure 2). A positive test is significantly associated with increased risk of anaphylaxis.⁶ Antihistamines should be stopped three days beforehand and systemic glucocorticoids seven days prior to testing. Patients who may not tolerate abstaining from treatment should have their results interpreted with caution. Patients with a strong history suggestive of cold urticaria but exhibiting negative results should have the test repeated.¹⁰ Ice-cube testing has the advantage of measuring the cold stimulation time, which refers to the shortest duration of cold exposure that results in wheal formation. The test is referred to as the cold stimulation time test (CSTT).

The critical temperature threshold (CTT) refers to the highest temperature required to produce a positive reaction (wheal formation). This can be measured using the commercially available Temp Test. The Temp Test (Courage & Khazaka electronic) uses the peltier effect and contains four thermal elements with temperatures ranging between 4 °C and 44 °C and a central microprocessor that controls the temperature.¹² The patient places the volar aspect of the forearm on an aluminium stencil on the top of the device for five minutes. The stencil produces the temperature range continuously. Reading is done after ten minutes. Both the CSTT and the CTT are recommended by the European Academy of Allergy and Clinical Immunology (EAACI) for determining the severity of disease and assessing treatment efficacy. The shorter the CSST or the higher the CTT, the higher the disease activity. Patients with severe disease can develop systemic symptoms and anaphylaxis during provocation testing;¹⁰ therefore, emergency treatment must always be available when performing these tests.

Differential blood count, erythrocyte sedimentation rate (ESR)

and C-reactive protein (CRP) measurement aid in ruling out underlying infections or autoimmune conditions that could trigger urticaria.¹ Routine testing with cold baths or cold packs is not recommended.⁵

DIFFERENTIAL DIAGNOSES

Cold urticaria may mimic several other disease entities, including physical urticarias such as heat, solar, aquatic and delayed pressure, infections (viral-induced urticaria), allergic reactions (from insect stings, drugs, food), lymphoproliferative diseases, leucocytoclastic vasculitis and cold agglutinin disease.^{4,5} Other differential diseases include mastocytosis, cold panniculitis, chilblain lupus erythematosus (CHLE), bradykinin-mediated angioedema and cryopyrin-associated periodic syndromes (CAPS) such as Familial Cold Auto-inflammatory Syndrome (FCAS), Muckle-Wells Syndrome and Neonatal-onset multisystem inflammatory disease (NOMID).

MANAGEMENT

The aims of managing cold urticaria include mainly trigger avoidance and symptom control. Recommendations include avoiding cold foods and drinks, caution while visiting areas with low ambient temperatures (skating rinks, supermarkets, etc) and avoiding winter sports such as skiing and swimming. Travel precautions should be undertaken when visiting caves and mountains. Care must be taken when the patient undergoes surgical procedures. The use of pre-warmed fluids and careful control of ambient theatre temperatures are advisable.⁵

Pharmacotherapy includes the use of second-generation antihistamines such as cetirizine and rupatadine in licensed doses. Two systematic reviews show up-titrating these drugs to four times the licensed dose, although off-label, is effective and without risk of adverse events.^{5,13} Temp Test provocation and determining the CTT are good indicators of the effectiveness of antihistamines.⁵ Omalizumab, an anti-IgE monoclonal antibody, is also effective in patients with antihistamine-resistant cold urticaria at a dose range of 150–600 mg/month.¹³ In omalizumab refractory patients, treatment options include cyclosporine, tricyclic antidepressants and immunosuppressive drugs (azathioprine, mycophenolate mofetil). Novel treatments currently in development include topical Syk inhibitors and the Interleukin-1 (IL-1) blocker, rilonacept. Biologics such as anakinra (an IL-1 inhibitor), etanercept (a TNF inhibitor), reslizumab (an IL-5 receptor inhibitor) and dupilumab (an IL-4 receptor inhibitor) show efficacy in some case reports.⁵

An Epipen is recommended for patients with cold urticaria.⁵ Cold desensitisation, although a poorly understood mode of therapy, has been shown to reduce the histamine response to a cold challenge. It involves progressively exposing the skin to cold in an attempt to induce cold tolerance and increase the time interval between wheal formation and cold exposure. Triggering anaphylaxis during cold desensitisation is a concern, however. These procedures are therefore discouraged in daily clinical practice.⁵

DISEASE PROGRESSION AND RESOLUTION

Disease progression is related to the severity of cold urticaria and tends to vary greatly between patients. In a ten-year

prospective study done at a tertiary hospital in Greece, the mean time to resolution of symptoms was 5.6 ± 3.5 years,² whereas the five- and ten-year resolution rates from a 20-year follow up study were 17.9% and 24.5% respectively. Notably, the absence of anaphylaxis with cold urticaria makes for a favourable prognosis.⁶

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

REFERENCES

1. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: Definition, classification and diagnosis of urticaria. *Allergy*. 2006;61(3):316–320. <https://doi.org/10.1111/j.1398-9995.2005.00964.x>.
2. Katsarou-Katsari A, Makris M, Lagogianni E, et al. Clinical features and natural history of acquired cold urticaria in a tertiary referral hospital: A 10-year prospective study. *J Eur Acad Dermatol Venereol*. 2008;22(12):1405–1411. <https://doi.org/10.1111/j.1468-3083.2008.02840.x>.
3. Siebenhaar F, Weller K, Mlynek A, et al. Acquired cold urticaria: Clinical picture and update on diagnosis and treatment. *Clin Exp Dermatol*. 2007;32(3):241–245. <https://doi.org/10.1111/j.1365-2230.2007.02376.x>.
4. Hochstadter EF, Ben-Shoshan M. Cold-induced urticaria: Challenges in diagnosis and management. *Case Reports*. 2013;2013:bcr2013010441. <https://doi.org/10.1136/bcr-2013-010441>.
5. Maltseva N, Borzova E, Fomina D, et al. Cold urticaria: What we know and what we do not know. *Allergy*. 2020;76(4):1077–1094. <https://doi.org/10.1111/all.14674>.
6. Yee CS, El Khoury K, Albuhairei S, et al. Acquired cold-induced urticaria in pediatric patients: A 22-year experience in a tertiary care center (1996–2017). *J Allergy Clin Immunol Pract*. 2019;7(3):1024–1031.e3. <https://doi.org/10.1016/j.jaip.2018.10.025>.
7. Gandhi C, Healy C, Wanderer AA, Hoffman HM. Familial atypical cold urticaria: Description of a new hereditary disease. *J Allergy Clin Immunol*. 2009;124(6):1245–1250. <https://doi.org/10.1016/j.jaci.2009.09.035>.
8. Tóth-Kása I, Jancsó G, Obál Jr F, Husz S, Simon N. Involvement of sensory nerve endings in cold and heat urticaria. *J Invest Dermatol*. 1983;80(1):34–36. <https://doi.org/10.1111/1523-1747.ep12530993>.
9. Sánchez J, Amaya E, Acevedo A, et al. Prevalence of inducible urticaria in patients with chronic spontaneous urticaria: associated risk factors. *J Allergy Clin Immunol Pract*. 2017;5(2):464–470. <https://doi.org/10.1016/j.jaip.2016.09.029>.
10. Magerl M, Altrichter S, Borzova E, et al. The definition, diagnostic testing, and management of chronic inducible urticarias – The EAACI/GA 2 LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy*. 2016;71(6):780–802. <https://doi.org/10.1111/all.12884>.
11. Visitsuntorn N, Tuchinda M, Arunyanark N, Kerdsonnuk S. Ice cube test in children with cold urticaria. *Asian Pac J Allergy Immunol*. 1992;10(2):111.
12. Siebenhaar F, Staubach P, Metz M, et al. Peltier effect-based temperature challenge: An improved method for diagnosing cold urticaria. *J Allergy Clin Immunol*. 2004;114(5):1224. <https://doi.org/10.1016/j.jaci.2004.07.018>.
13. Kulthanan K, Hunnangkul S, Tuchinda P, et al. Treatments of cold urticaria: A systematic review. *J Allergy Clin Immunol*. 2019;143(4):1311–1331. <https://doi.org/10.1016/j.jaci.2019.02.005>.