CASE REPORT

Cold-induced urticaria: challenges in diagnosis and management

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SUMMARY

Cold-induced urticaria (CU) is a chronic physical urticaria that can be hard to diagnose and manage. Symptoms of CU can vary from mild localised urticaria, angio-oedema to anaphylaxis. CU may be induced by a wide range of cold triggers from aquatic activities to ingestions of cold substances. This exemplifies the importance of accurate diagnosis and management of patients with CU. We present three cases of CU that demonstrate the variability in triggers and clinical presentation.

BACKGROUND

Cold-induced urticaria (CU) is a subtype of physical urticaria initially described by Boudron in 1866.[1] Physical urticaria account for 25% of all cases of chronic urticaria (ie, urticaria that lasts at least 6 weeks). Six to 34% of individuals with physical urticaria have CU.[2 3] Naturally, higher frequency tends to be observed in areas with colder environments.[3] CU consists of the development of localised or diffuse urticaria, angio-oedema and occasionally systemic symptoms secondary to exposure to a cold stimulus. Stimuli include cold environments, aquatic activities, ingestion of cold foods and liquids and handling cold objects. The frequency is approximately the same in men and women; and while it occurs more commonly in young adults (20–30 years), the age range is quite broad (3 months to 74 years). The mean duration of this type of chronic urticaria is 4.8–9.3 years with 50% improving within approximately 5 years.[2–4]

Given the different possible cold triggers of CU, a detailed history and the use of confirmatory tests are required to appropriately establish the diagnosis. The cold stimulation test (CST) is the main test used to diagnose CU, also known as the ice cube test. The CST is considered positive if a cold stimulus of 0–4°C (eg, an ice cube in a plastic bag) placed on the volar surface of the forearm for 5 min triggers the development of a weal after rewarming for 5–10 min. The test may be then repeated at shorter intervals to establish minimum time required for induction of a weal (cold stimulation time test). A negative test is defined when no weal develops after 5–10 min and this has been described in atypical forms of CU.[5]

With cold stimuli being very common, underdiagnosis or misdiagnosis of this type of urticaria could lead to a significant impact on the quality of life of patients.[6 7] Given that management strategies differ according to reaction severity, clinician's should be aware of the different clinical presentations of CU.[8] The three paediatric cases of CU present in this paper help demonstrate the variability of this type of urticaria and the importance of appropriate diagnosis and management.

CASE PRESENTATION

Case 1

The first case is an 8-year-old boy living in Montreal, Canada, who presented with recurrent hives for the last 2 years. His first episode occurred when swimming in a pool, as he exited the water and was exposed to cold air. His parents attributed this to viral illness. At the start of the next winter season, he developed hives at sites of skin exposed to cold. There were no other identifiable triggers of his hives including stress, exercise, food, contact or heat. He had no angio-oedema, difficulty in breathing or systemic symptoms. He was a previously healthy boy with no allergies, asthma or eczema. He had no history of hives, thyroid or autoimmune diseases and no recent travel outside of Canada. His family had no history of hives, thyroid or autoimmune diseases. He was diagnosed with CU based on his history and a positive ice cube test. He was treated with second generation antihistamines to control his symptoms during the cold seasons. In addition, he was advised to limit skin exposure (through protecting clothing) during cold weather.

Case 2

The second case is 4-year-old boy who was referred to the allergy clinic for mouth itchiness persisting for a month. The patient reported of tongue pruritus mainly in the evening that developed shortly after returning home after playing outside. There was no specific trigger associated with his symptoms. The patient developed an episode of hives in the winter shortly after cold exposure (figure 1). He was healthy previously. Other than positive dermatographism, the patient had a normal physical exam. His ice cube test was positive after 10 min and he was diagnosed with CU. Subsequently, he was treated with reactine (cetirizine) daily with a good response.

Case 3

The third case is a 12-year-old boy who presented with three episodes of urticaria over a few months developing within minutes after swimming in a lake/pool. He presented initially with abdominal pain that developed within minutes after he dived into a lake. A few minutes after exiting the water, he lost consciousness and had a generalised seizure that lasted a few seconds. He had neither fever nor a preictal or postictal period. There was no previous

To cite: Hochstadter EF, Ben-Shoshan M. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-010441

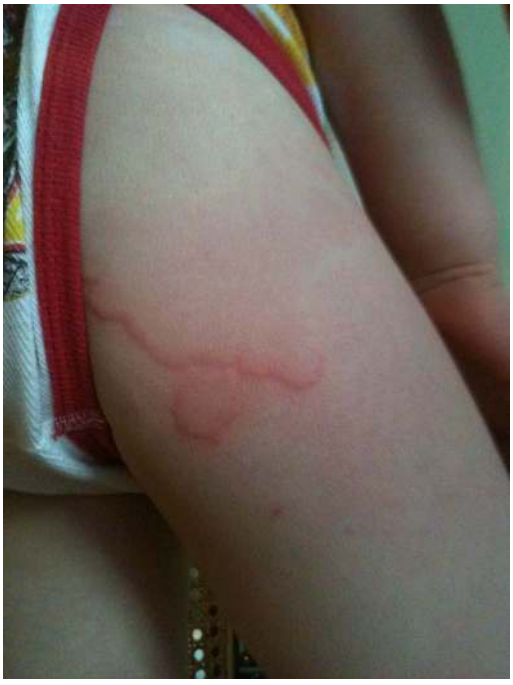

Figure 1 Generalised urticaria developing after exposure to cold.

history of seizures and no other cause of seizures was identified. His mother did not note any swelling of his tongue or difficulty in breathing. The second episode occurred a few minutes after swimming in a pool where he developed hives for 10 min that gradually disappeared. His third episode occurred when swimming in a lake where he developed oedema of his arms and knees that was painful. He had a positive ice cube test at 5 and 10 min (figure 2A,B). The patient's mother was concerned that he reacted to the algae or fish in the water, but skin testing was negative for fish, crustaceans and algae. Owing to the severity of his CU, he was advised to take second generation antihistamines 2 days prior to swimming and to avoid abrupt cold exposure (eg, jumping in a pool). Further, given his systemic symptoms, he was prescribed an epinephrine autoinjector and advised to have it available at all times.

INVESTIGATIONS

Given that history, physical signs and ice cube test are consistent with CU, no further investigations are needed in the cases described. However, in the absence of a clear physical trigger, further testing may be required to establish the diagnosis. Baseline complete blood count with differential is recommended in cases on chronic urticaria. Abnormal results might suggest the presence of an infectious or inflammatory process. Inflammatory markers such as erythrocyte sedimentation rate and C reactive protein can be useful in cases of a suspected autoimmune disease with the addition of antineutrophil antibody, rheumatoid factor, complement 3 and 4 (C3/C4), CH50, antidouble stranded DNA, antithyroglobulin/antithyroid peroxidase antibodies and antismooth muscle antibody. If angio-oedema is a presenting symptom especially in the presence of a similar family history, C1 esterase inhibitor level and function as well as factor XII mutations should be assessed to rule out the possibility of hereditary angio-oedema.[5] If underlying allergies are suspected, skin prick testing and specific IgE levels may help identify possible triggers.

Cases of autoimmune chronic urticaria could be diagnosed through the use of autologous serum skin test and histamine release assay and through the assessment of CD63 levels that mark basophil activation.[9–11] Finally, in the absence of an identified trigger and the continuation of hives, the diagnosis of chronic spontaneous urticaria may be applied.[9–11]

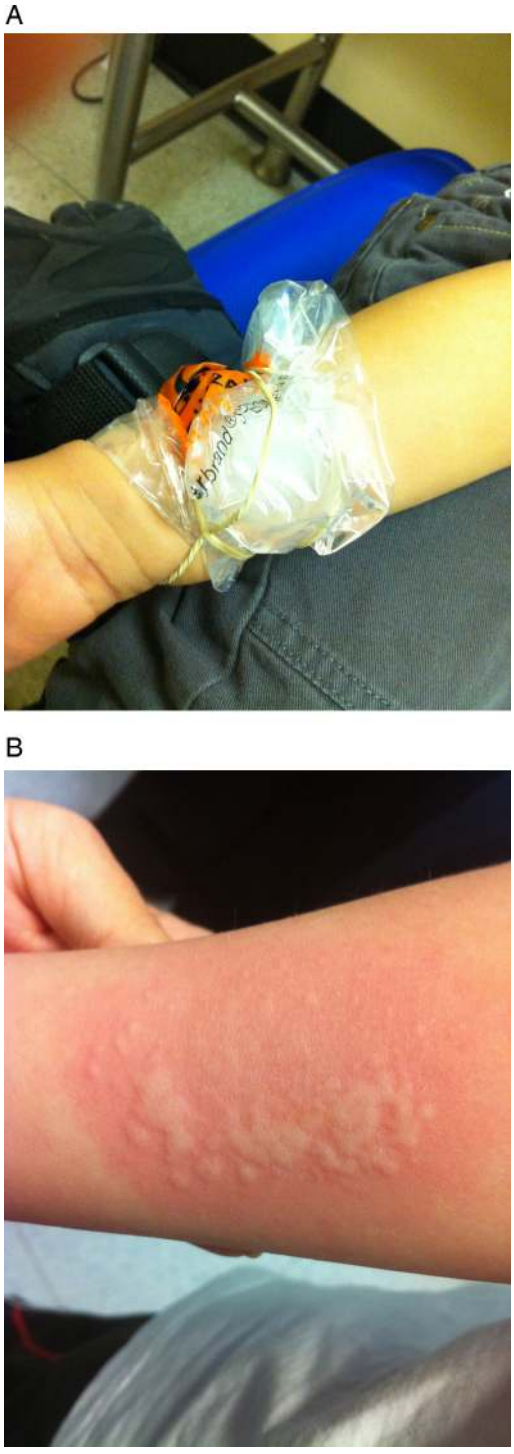

Figure 2 (A) Cold stimulation test (ice cube test): ice placed on the patient's volar surface of the forearm. (B) Positive ice cube test: urticaria after 5 min of ice placement and 5 min of rewarming.

DIFFERENTIAL DIAGNOSIS

When diagnosing CU, it is important to rule out other possible causes of urticaria. These include viral-induced urticaria, allergic reactions (food, medications, bug bites) and other types of

physical urticaria. Given the history of reactions, infectious and allergic triggers unlikely contribute to the patient's symptoms. Physical urticarias (also referred to as inducible urticarias) include mechanical, cold, solar, heat, delayed pressure, aquagenic and vibrative urticarias.[2] Once the trigger of cold is identified, the differential diagnosis of CU includes primary idiopathic, secondary, atypical and familial syndromes.[4 12–14]

In the three cases described, the patients did not have symptoms of fever, joint involvement or hearing loss and the urticaria did not develop during early childhood. Hence, familial syndromes including rare cases of phospholipase Cγ-2 gene mutations[15] and mutations in cold-induced auto-inflammatory syndrome-1 gene resulting in cryopyrin-associated periodic syndrome[16 17] are unlikely.

TREATMENT

It is important to reassure patients on the usually benign course of the disease and to protect body surfaces when cold exposure is inevitable as well as to avoid rapid exposure to cold water. Patients are usually advised to keep an urticaria activity score diary[18] to characterise cold triggers and control of disease activity. In severe cases, it is important to have an action plan in case of systemic reaction including the need to have an epinephrine autoinjector available and prompt use if necessary.

Medication of choice is antihistamines, preferably second generation, which will control the hives and itchiness in most cases.[5 19] In 2008, at the Third International Meeting on Urticaria, it was established that antihistamine dose could be safely increased up to fourfold if symptoms persist before switching to other therapies.[20 21]

Although studies suggest that cold tolerance induction may be an effective strategy to control symptoms, it is rarely used due to poor compliance.[22]

OUTCOME AND FOLLOW-UP

All three cases were managed with low to high doses of antihistamines. The third patient was prescribed an epinephrine autoinjector, but had achieved control with the use of antihistamines and did not require the use of the autoinjector.

DISCUSSION

The three cases presented in this paper draw attention to the diagnostic and management challenges that physicians face when treating patients with CU.

Primary acquired cold urticaria is the most common type of CU. Diagnosis of acquired CU is established by an immediate positive CST. Familial forms of CU are rare and usually characterised by earlier onset and the involvement of other systems.[15–17] Secondary cold urticaria is less common and develops secondary to a systemic infectious or autoimmune disease. Similar to primary cold urticaria, secondary cases are characterised by the development of hives after cold exposure and an immediate positive CST. Causes of secondary CU include cryoglobulinemia with or without malignancies, infections such as HIV, syphilis, hepatitis, parasites and bacterial infections. In addition, leucocytoclastic vasculitis and cold agglutinin disease may contribute to a similar clinical presentation.[5]

Atypical cold urticaria has similar presentation as the other types of cold urticaria, however, it usually involves more severe reactions including symptoms such as hypotension. Patients with atypical cold urticaria have a negative CST. Atypical cold urticaria can be subclassified into several forms including systemic, localised, cold-induced cholinergic urticaria, cold dependent dermatographism, delayed cold urticaria and localised cold-reflex urticaria.[23]

Familial conditions with CU include familial cold autoinflammatory syndrome , delayed cold urticaria with autosomal dominant inheritance and Meckel-Wells syndrome.[13 24 25]

The cases presented can be classified based on symptom severity.[23] Type I cold urticaria is localised urticaria and/or angio-oedema. Type II is generalised urticaria and/or angio-oedema without hypotensive or respiratory symptoms. Type III is the most severe form and presents with severe systemic reactions with greater or equal to one episode suggesting respiratory distress (wheezing or shortness of breath) or hypotension (dizziness, sensation of fainting, disorientation or shock). Based on this classification, our first and second cases would be considered mixed type I and II as they presented with both local and diffuse hives. The third case is clearly type III as the patient presented with severe systemic symptoms. Determining reaction severity is crucial as it might guide patient management. Cases consistent with type III should be prescribed an epinephrine autoinjector, while type I and/II may be managed through extreme cold protection and the use of antihistamines alone.

In a review of 30 children (18 and under) with CU, it was found that 36.7% of the patients developed a type III reaction with 45.5% of them experiencing respiratory distress and 72.7% developing a decrease in the level of consciousness. In all severe type III reactions, the main trigger was aquatic activities. The group was also shown to have a higher prevalence of atopy.[8] The only predictor of anaphylaxis in children with CU was a previous history of a systemic reaction to cold exposure. Further, the authors indicate that according to their experience, patients with a history of mild reactions (few hives) with swimming often wish to continue participating in aquatic activities and are at a lower risk for anaphylaxis.[8] Recently, a case of CU leading to anaphylaxis was described in a 9-year-old girl who developed generalised hives and syncope while swimming in cold water.[26] Thus, while rare, life-threatening reactions to cold may occur and patients and caregiver preparedness should be maintained in these cases including the use of an autoinjector.

The pathogenesis of CU is unclear although it is has been suggested that IgE antibodies react against specific skin antigens at the appropriate temperature causing the release of histamine and other inflammatory mediators.[14 27 28]

As discussed, management involves education and avoidance of triggers. In patients with severe systemic reactions, emphasis is on the avoidance of aquatic activities that could create severe reactions. A spectrum from low to high dose antihistamines can be used.[20 21 29]

While omalizumab has been shown to be effective in case reports, larger randomised controlled trials are needed to establish its effect.[30 31]

In conclusion, the cases presented provide three different scenarios of CU and exemplify diagnosis and management challenges involved in the care for these patients. Future studies are required to determine the pathophysiology and preferred management of CU. It is crucial to develop guidelines and educational programmes that would increase the overall awareness to the management of this important condition.

Learning points

- Cold-induced urticaria is a type of physical urticaria that can vary in presentation from mild, localised urticaria and/or angio-oedema to generalised urticaria to severe systemic symptoms that can lead to death.
- Triggers of cold urticaria can vary between patients and can be secondary to ingestion of cold substances, aquatic activities, exposure to cold environments or objects.
- Diagnosis of cold-induced urticaria involves an accurate history and use of the cold stimulation test (ice cube test) to assess the development of a weal secondary to cold exposure.
- While most cold urticaria are acquired, secondary forms as well as atypical and familial conditions must be ruled out.
- Treatment of cold urticaria involves education, avoidance of triggers and use of antihistamines and an epinephrine autoinjector in severe cases.

Contributors All authors contributed to this paper (including preparation and revision of the manuscript) and have approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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