CASE REPORT

The association of cholinergic and cold-induced urticaria: diagnosis and management

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SUMMARY

Physical urticaria is often challenging to diagnose and manage. We present a case of both cholinergic and cold-induced urticaria and discuss the diagnosis and management strategies of these two important conditions.

BACKGROUND

Chronic urticaria (CU) is defined by the presence of wheals occurring over a period of at least 6 weeks.¹ It is a common and debilitating disease. The lifetime prevalence of CU is 3% in adults and 0.1–0.3% in children.² When diagnosing CU, it is important to identify its many subtypes, which fall into two main groups: spontaneous urticaria and inducible urticaria (eg, physical urticarias and cholinergic urticaria). Physical urticaria has been reported to be responsible for up to 25% of cases of CU³ and is induced by physical factors. Physical urticaria subtypes include dermatographism, cold contact, heat contact, delayed pressure, solar and vibratory urticaria.^{3–4} Cold-induced urticaria accounts for up to one-third of all physical urticarial cases.⁵ Cold urticaria is characterised by localised or diffuse urticaria (which can be accompanied by angioedema) within minutes after exposure to contact with cold temperature (object, air or liquid). It may evolve into systemic symptoms and anaphylaxis with extensive cold contact, such as swimming in cold water, in up to one-third of children.⁶ Patients with cold urticaria should avoid ice cold drinks and food because of reported cases of localised angio-oedema of the oropharynx.^{3–6}

Cholinergic urticaria is classified as an inducible form of urticaria and not as a subtype of physical urticaria because it is triggered by an increase in the core temperature of the body and not by exogenous physical triggers acting on the skin.⁷ It is reported to occur in 4–11% of all young adults.^{7–9} The main triggers of this form of urticaria include exercise and hot showers.³ Other eliciting factors such as emotional stress and spicy food have been reported.¹⁰ Cholinergic urticaria represents 5% of all cases of chronic urticaria.³ The other inducible types of urticaria are aquagenic, contact and exercise-induced urticaria/anaphylaxis.^{3–7} Cholinergic urticaria presents as itchy pinpoint non-follicular, mainly located on the trunk and upper extremities and the symptoms are aggravated by exercise.^{10–12} This differs from exercise-induced urticaria/anaphylaxis, which manifests as larger wheals frequently evolving into anaphylaxis.⁴ The skin lesions in cholinergic urticaria appear immediately, within a few minutes after

exercise or passive warming, and typically last 15–60 min.³ This again differs from exercise-induced urticaria/anaphylaxis, which is induced by exercise only and not by passive warming.^{3–4}

Diagnosis of cold urticaria and cholinergic urticaria is made by collaborating patient's history, physical examination and provocation tests. A thorough history must be obtained to include all possible eliciting factors and the presence of more than one type of chronic urticaria.^{3–10} The case presented in this paper demonstrates the co-occurrence of two types of inducible urticaria: cold and cholinergic, in a paediatric patient.

CASE PRESENTATION

A 16-year-old boy was referred to the allergy clinic for recurrent urticaria for the last 2 years. He developed hives in association with exposure to cold air and with swimming. In addition, he also developed a generalised pruritic papular rash immediately after exercise, independent of cold exposure. His symptoms occurred throughout the year as well as following hot baths. There was no other systemic involvement, such as respiratory, gastrointestinal or cardiovascular symptoms. He did not present with joint involvement. He was not taking any medication and had not been treated for these episodes. The family history was unremarkable; however, his mother was known to have a benign thyroid nodule.

INVESTIGATIONS

The patient's physical examination was normal except for dermatographism. His ice cube test was positive after 15 min when he developed hives localised at the site of the ice cube (figure 1).

A diffuse papular and pruritic rash sparing his face was reproduced during an exercise challenge test (climbing stairs for 15 min; figure 2A, B). Owing to practicality issues with whole body immersion in a hot bath, a challenge with hot (42°C) running water on the patient's hand for 10 min was conducted.¹³ There have been cases of systemic reactions with this challenge, therefore caution must be taken if performing this test; it is usually not preferred.¹⁴ The patient presented with local itchiness and papular rash within 5 min of the challenge.

The laboratory investigations in our case revealed normal complete blood count, C reactive protein (CRP), tryptase and antithyroid peroxidase antibody.

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Figure 1 Positive ice cube test.

DIFFERENTIAL DIAGNOSIS

Allergic urticaria induced by food, medication or insect stings is unlikely in the case presented, given the absence of a temporal association with such triggers in the history.

Once the trigger of cold is identified the differential diagnosis of CU includes primary idiopathic, secondary, atypical and familial syndromes.^{9 13–17} In the case described, the patient 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 C γ 2 gene mutations and mutations in cold-induced autoinflammatory syndrome-1 gene (CIAS1) are unlikely.^{17–20}

Cholinergic urticaria and exercise-induced urticaria/anaphylaxis are two different entities that need to be differentiated. Given that our patient had a history of developing a pruritic pinpoint rash after taking warm showers and after exposure to

running hot water as well as a positive exercise challenge, his most likely diagnosis is cholinergic urticaria. Since his symptoms were restricted to the skin only, the diagnosis of exercise-induced anaphylaxis is unlikely.

TREATMENT

Treatment options for physical urticarias and cholinergic urticaria rely on avoidance of the triggers and inhibition of mast cell mediators such as histamine with a second-generation non-sedating H1 antihistamine.³ Another important factor to consider in cold urticaria is the impact of the wind chill factor in colder climates.¹⁰ Given that our patient reacts to both cold and warm stimuli, the treatment is especially challenging. We recommended desloratadine 5 mg once daily and suggested doubling the dose before physical activities, especially when performed in a cold environment.

OUTCOME AND FOLLOW-UP

In a follow-up 6 months later, the patient reported substantial improvement with tolerability for most physical activities apart from swimming in non-heated pools, which was not advised.

DISCUSSION

The case presented exemplifies the complexities related to the diagnosis and management of patients with inducible urticaria. Our case is especially interesting as it involves the management of two concurrent inducible forms with treatment strategies that do not necessarily overlap.

Our patient presented with the most common combination of inducible forms of urticaria: cold and cholinergic.¹⁷

In a study of 220 patients with cold urticaria, it was found that 21% had dermatographism and 8% had cholinergic urticaria. However, other forms of inducible urticaria rarely occur concurrently.¹⁷ The diagnosis of these forms of inducible urticaria requires the collaboration of suggestive clinical history and positive confirmatory tests. The diagnosis of cold-induced urticaria is confirmed in the presence of a positive ice cube test as demonstrated in our case. Diagnosis of cholinergic urticaria involves a two-step approach with an exercise and hot bath provocation test.^{3 10} The initial step is moderate exercise appropriate to the patient's age, to the point of sweating and 15 min beyond.³ This can be done on a treadmill, stationary bicycle or

Figure 2 (A and B) Positive exercise challenge.

using stairs. A positive test involves the appearance of the typical pruritic pinpoint rash after 10 min of the exercise challenge. Once this is positive, the second step, which is the passive warming test with a hot bath should be performed, at least 24 h later.³ The goal is to raise the body temperature by at least 1°C and induce the typical rash. This can be carried out by partial submersion of the patient in a 42°C bath for up to 15 min while recording body temperature.¹⁰ This test, along with history, is the differentiating point between cholinergic urticaria and exercise-induced anaphylaxis/urticaria. Our patient clearly meets the diagnostic criteria of both cold and cholinergic urticaria. Routine laboratory tests are suggested if there is suspicion of an underlying disease³ and for ruling out possible differential diagnoses, if indicated.¹⁰ These tests include a complete blood count and differential, inflammatory markers such as CRP and erythrocyte sedimentation rate and cryoproteins.¹⁰

The mechanisms underlying the development of these inducible forms of urticaria are currently unclear. It has been suggested that cold urticaria develops when IgE antibodies react against specific skin antigens at the appropriate temperature causing the release of histamine and other inflammatory mediators.^{13 21 22} Cholinergic urticaria is suggested to develop due to immediate-type allergy to autologous sweat antigens²³ or due to IgE that develops in response to antigens secreted by *Malassezia globosa* contained in human sweat.²⁴ However, cholinergic urticaria is sometimes accompanied by anhidrosis, suggesting that sweat may not always be necessary and that other mechanisms may be involved in the development of cholinergic urticaria.²⁵

The management of inducible urticaria is complex due to poor response to antihistamines, the difficulty of avoiding physical triggers and poor rates of resolution.^{26 27} It is especially important to appropriately manage the combination of inducible forms.^{17 28 29} While the management of cold-induced urticaria involves protection against cold exposure and use of warm clothing, these exact measures may induce cholinergic urticaria. Hence, patients experiencing both forms of urticaria need to tightly supervise their body exposure to avoid extreme temperature exposure and use antihistamines regularly.³⁰ Patients with cold-induced urticaria should avoid ice cold drinks and food to prevent oropharyngeal oedema as well as extensive cold contact (eg, swimming in cold water).³ In rare cases of systemic reactions to cold, an epinephrine autoinjector should be prescribed as well.⁶

Before anti-IgE treatment, many patients suffered from their inducible urticaria for years and had numerous unsuccessful therapies. The overall excellent responses to omalizumab treatment reported in physical urticaria^{31 32} suggest that the patient's quality of life might improve substantially with this relatively safe treatment. Other options for both types of urticaria include rapid desensitisation with autologous sweat^{22 25} and cold induction.²⁷ However, these treatments are not commonly used due to low compliance. In addition, anticholinergic agents including injection of botulinum toxin to decrease sweating were reported in case reports to benefit patients with cholinergic urticaria.³³ Although antileukotriene therapy might be effective in some forms of chronic urticaria, to date it has been unhelpful in forms triggered by exercise.³⁴ In conclusion, inducible urticarias impose diagnostic and management challenges especially when combined. Further research is required to explore the aetiology of these forms and to establish the optimal management strategy.

Patient's perspective

Establishing the correct diagnosis for my symptoms and identifying the triggers as well as reassuring on the benign nature of my condition helped me cope more efficiently with my symptoms and gain better control of my inducible urticaria.

Learning points

- ▶ Cold-induced and cholinergic urticaria are two types of inducible urticaria that can vary in presentation and often coexist.
- ▶ Diagnosis of cold-induced urticaria involves an accurate history and use of the cold stimulation test (ice cube test).
- ▶ Diagnosis of cholinergic urticaria involves an exercise challenge test as well as a passive warming test.
- ▶ Treatment of both conditions involves education, trigger avoidance and use of antihistamines.

Competing interests MB-S is the consultant for Sanofi and Novartis and is the recipient of the FRSQ junior 1 award.

Patient consent Obtained.

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