

Cold, cholinergic and aquagenic urticaria in children: presentation of three cases and review of the literature

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SUMMARY: Arıkan-Ayyıldız Z, Işık S, Çağlayan-Sözmen Ş, Karaman Ö, Uzuner N. Cold, cholinergic and aquagenic urticaria in children: presentation of three cases and review of the literature. Turk J Pediatr 2013; 55: 94-98.

Urticaria can be induced with a wide variety of environmental stimuli, such as cold, pressure, vibration, sunlight, exercise, temperature changes, heat, and water. Urticaria caused by physical factors has been reported as the cause of 6-17% of the chronic urticaria in children. We present three cases here - cholinergic, cold and aquagenic urticaria - in which the diagnosis was proven with exercise, ice-cube and water provocation tests, respectively.

Key words: cholinergic urticaria, aquagenic urticaria, cold urticaria, children.

Urticaria can be induced by a wide variety of environmental stimuli, such as cold, pressure, vibration, sunlight, exercise, temperature changes, heat, and water. Urticaria caused by these physical factors has been reported as the cause of 6-17% of the chronic urticaria in children¹. Previous terminology regarding physical urticaria included all urticaria subtypes that are triggered by physical factors². However, in the recent classification, dermatographic urticaria, being the commonest form of physical urticaria in children and adults, cold urticaria, delayed pressure urticaria, and solar urticaria are included in physical urticaria, while cholinergic urticaria (CU), aquagenic urticaria (AU) and exercise-induced urticaria/anaphylaxis are classified as other subtypes of urticaria³. In most of these subtypes, urticaria appear rapidly after exposure and last for a short time, but there is enough variability in presentation to present a dilemma in diagnosis⁴. Because of the overlap of triggers and coexistence of multiple subtypes, diagnostic testing should be encouraged in each patient suspected with these subtypes of urticaria.

In this report, we describe three cases of urticaria - cold, cholinergic and aquagenic urticaria - in which the diagnosis was proven with the recommended diagnostic tests in all cases.

Case Reports

Case 1

A 14-year-old boy was admitted to our hospital with a two-year history of recurrent episodes of generalized small round-shaped wheals with severe itch induced by exercise and bath. He had asthma for approximately four years, and it was unaffected by triggers such as hot baths, exercise and emotional factors. His physical examination was normal. Laboratory data were within normal limits except for skin prick test (SPT). SPT was positive for olea and house dust mites. Ice-cube challenge and water challenge tests were performed and were negative. The challenge with exercise for 10 minutes induced pruritus and hives (Fig. 1). Management of his condition involved avoidance of hot bath, heavy exercise during hot weather, and emotional strains and pharmacotherapy with second-generation H1 antihistamines if needed.

Case 2

An 11-year-old boy was admitted to our hospital with a one-year history of urticarial rash on parts of his trunk after exposure to cold. There were no associated findings such as angioedema, hypotension or respiratory symptoms. He had no recent infections. On initial physical examination, crusted papules were present on his legs. He also had chronic pruritic eczema occurring on the flexural part



Figure 1. Wheals on the trunk of the first patient after exercise testing.

of his extremities during the summer. His sister had allergic rhinitis and his aunt had atopic dermatitis. His laboratory examination for complete blood count, urine analysis, C-reactive protein, erythrocyte sedimentation rate, basic biochemistry tests, thyroid function tests, and anti-thyroid autoantibodies were normal. Cryoglobulins, antinuclear antibodies and HBsAg were all negative. There were no parasites or eggs in the stool sample. His skin test was positive for grass pollens. Level of total immunoglobulin (Ig)E was 402 IU/ml. On the basis of his symptoms and laboratory investigations, clinical diagnosis of acquired cold urticaria and atopic dermatitis was made. An ice-cube test was performed on the volar forearm and diagnosis was confirmed with a large palpable wheal (Fig. 2). We prescribed a nonsedating second-generation H1 antihistamine for the patient, and his symptoms resolved completely after treatment.



Figure 2. Positive ice cube test of the second patient.



Figure 3. Wheals on the arm of the third patient after water provocation test.

Case 3

An eight-year-old boy presented with wheals appearing after taking a shower or swimming in the pool or sea, regardless of the temperature. Wheals were small in nature and appeared predominantly on the trunk. Lesions appeared within 10 minutes of contact with water. These pruritic hives lasted for 30 minutes and resolved spontaneously. His symptoms were not triggered by other conditions such as cold weather, exercise, sweating, stress, or sunlight. He was also allergic to house dust mites and had persistent allergic rhinitis. He had no family history of atopy. Physical examination was unremarkable except dermographism, which was elicited with stroking the skin with a tongue blade. The diagnosis of AU was confirmed by applying a compress soaked in water at body temperature for 20 minutes. Response to test was positive with induction of wheals on the contact area (Fig. 3). Ice-cube test and exercise test were negative, and laboratory tests including complete and differential blood count, liver function tests, erythrocyte sedimentation rate, and thyroid function tests were normal. He was prescribed an antihistamine (rupatadine) daily, and his symptoms were under control after one month.

Discussion

Urticaria caused by physical factors is a relatively common cause of chronic urticaria in childhood and affects quality of life in most of the cases². Of all the diagnostic procedures of urticaria, the most important is to obtain a

Table I. Recommended Diagnostic Tests in Urticaria Subtypes

Subtypes	Routine diagnostic tests*	Extended diagnostic program†	
Cold contact urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)		Differential blood count, ESR, CRP, cryoproteins, infections work-up
Delayed pressure urticaria	Pressure test (0.2-1.5 kg/cm ² for 10-20 min)		None
Heat contact urticaria	Heat provocation and threshold test (warm water)		None
Solar urticaria	UV and visible light of different wave lengths		Rule out other light-induced dermatoses
Dermographic urticaria	Elicit dermatographism		Differential blood count, ESR/CRP
Aquagenic urticaria	Wet cloths at body temperature applied for 20 min		None
Cholinergic urticaria	Exercise and hot bath provocation		None
Contact urticaria	Prick/patch test read after 20 min		None
Exercise-induced anaphylaxis/urticaria	According to history exercise test with/without food but not after a hot bath		None

* recommended. † suggested. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein.

detailed history including all possible eliciting factors and significant aspects of the nature of the urticaria³. The second step is the physical examination of the patient, including a test for dermatographism, and subsequent diagnostic steps will depend on the nature of the urticaria. Recommended diagnostic tests in specific subtypes of urticaria are summarized in Table I³. We presented three subtypes of urticaria here: cholinergic and cold urticaria, which are relatively common, and AU, which is seen rarely in children. Our patient is the third reported case of AU from Turkey.

Cholinergic urticaria (CU) is one of the subtypes of urticaria characterized by small and pruritic wheals that follow sweating events and elevation in body temperature such as during physical exercise, intake of spicy foods and emotional strains⁵. CU is believed to account for approximately 30% of all cases of urticaria caused by physical factors⁶. The CU pathogenesis is still poorly understood, but its diagnosis is not difficult because of characteristic clinical manifestations. Recommended diagnostic tests in CU are exercise and hot bath provocation tests³. We performed exercise provocation test for diagnosis of the first patient, which was positive. We ruled out exercise-induced urticaria because our patient's hives were not triggered by exercise alone but also hot baths. CU may be associated with other subtypes of urticaria, such as dermatographic and aquagenic urticaria, so detailed history for triggers and diagnostic testing are important for the diagnosis of each subtype^{2,7}. Identification and avoidance of known triggers are the first steps in the management of CU. Medical therapy consists of oral second-generation H1 antihistamines, danazol and omalizumab in refractory cases⁴.

Cold urticaria is a subtype of physical urticaria and is characterized by pruritic wheals and/or angioedema after cold exposure. Triggers of cold urticaria include cold beverages, cold air and cold objects. They induce release of histamine and proinflammatory mediators from skin mast cells and cause wheal and flare reaction⁸. Cold urticaria can be classified as acquired and familial. There were no similar symptoms in family members of our case, so our patient was diagnosed as acquired cold urticaria. Acquired cold urticaria is subdivided into primary

(unknown etiology) or secondary (due to an underlying cause). The secondary form can be associated with viral, parasitic or bacterial infections, cryoglobulinemia and autoimmune diseases^{9,10}. Our patient's laboratory findings were all normal except elevated IgE and skin test positivity. Increased levels of IgE can be found in up to 70% of cold urticaria patients, and up to half of patients are atopic^{9,10}. If the patient's history is compatible with cold urticaria, diagnosis can be confirmed with ice-cube test¹¹. We placed an ice cube on the volar forearm of the patient for five minutes, and typical urticaria occurred in minutes after removal of the ice cube. A thermoelectric device (TempTest® Emo Systems GmbH, Berlin, Germany) can also be used for diagnosis and determination of temperature and time thresholds for the patients¹². In this case, the lesions were confined to cold exposure areas only, but some patients can experience systemic reactions as anaphylaxis with extensive cold contact. Temperature thresholds can help clinicians to predict risky situations and assess for type of treatment (need for an epinephrine auto injector)¹³. We educated the family regarding cold avoidance and prescribed a nonsedating second-generation H1 antihistamine with standard dose for primary prophylactic therapy⁹.

Aquagenic urticaria (AU) is a rare form of urticaria, in which contact with water, regardless of its temperature and source, evokes wheals⁴. Fewer than 100 cases are reported in the literature, which include two adolescents from our country^{14,15}. It is more common in women than in men and appears usually in puberty, but cases presenting in childhood are also reported^{4,14,16}. Most cases are sporadic, but familial cases are also reported^{17,18}. Small pruritic wheals appear after exposure to water, and they are usually located on the neck, upper trunk and arms. Water challenge test performed at body temperature for 20 minutes is recommended for diagnosis of AU. Diagnosis of AU requires exclusion of other types of urticaria, so exercise test for CU and ice-cube test for cold urticaria should be performed. Our patient's (Case 3) ice-cube test and exercise test were negative, and we excluded these subtypes. Antihistamines are required for treatment of AU, but response may vary, and ultraviolet (UV) radiation therapy may be

required for refractory cases.

We observed atopy in our three patients, but evident association between atopy and these subtypes of urticaria has not been found to date. However, it has been observed that history of allergic conditions was associated with poorer prognosis of physical urticaria in childhood².

These three cases show that detailed history for triggers and diagnostic tests for diagnosis and exclusion of relevant subtypes of urticaria are needed for obtaining an accurate diagnosis. Because interventions may differ between the different subtypes, accurate diagnosis will aid successful management of the symptoms.

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