

Review of Physical Urticarias and Testing Methods

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Abstract

Purpose of Review This review aims to update the information available on the prevalence, clinical picture, diagnostic methods, and treatment of urticarias induced by external physical stimuli.

Recent Findings Physical urticarias are present in up to 5% of the general population, and in 10 to 50% of patients with chronic urticaria. Recent investigations have provided evidence that the presence of physical urticaria alone or when comorbid with chronic spontaneous urticaria is associated with a worse prognosis and duration.

Summary Most frequent subtypes of physical urticaria are dermographism and delayed pressure urticaria. The diagnosis is established through specific provocation tests and the management encompasses avoidance measures, pharmacologic therapy with nonsedating antihistamines, and alternative medications in refractory cases.

Keywords Angioedema · Chronic urticaria · Dermographism · Inducible urticaria · Physical urticaria · Urticaria

Introduction

In contrast to chronic spontaneous/idiopathic urticaria, the term inducible urticaria is generally used when a specific trigger can be linked to the development of chronic urticaria (CU), whereas physical urticarias (PU) are a subtype of inducible urticarias whose induction is associated with a specific physical factor.

Physical urticarias are defined in the current international guidelines as a group of diseases in which wheals and/or angioedema are reproducibly induced by external physical stimuli [1•]. Among them, dermographism, delayed pressure urticaria (DPU), cold, heat, solar, and vibratory urticaria/angioedema are included [2•]. On the other hand, aquagenic and cholinergic urticaria are inducible forms of CU that presently are not included into the group of PU because in them wheal formation is not induced by a physical stimulus. As in other types of CU, the pathogenesis of PU depends on the release of histamine and other inflammatory mediators from activated cutaneous mast cells.

In this article, an update of the current knowledge on prevalence, pathogenesis, clinical picture, diagnostic methodology, and management of the different subtypes of physical urticaria is presented.

Prevalence of Physical Urticarias

PU have been estimated to be present in up to 5% of the general population, and in 10 to 50% of patients with CU, a PU

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component (most commonly symptomatic dermatographism and DPU) is present [3]. In fact, it is important to recognize that a combination of PU and chronic spontaneous urticaria (CSU) is often observed, whereas an individual patient may show simultaneously two or more inducible forms of urticaria [4]. Patients with CSU with a component of PU have a worse prognosis, with longer disease duration [5, 6, 7]. For example, in a study by Kozel and coworkers, the remission rate in patients with comorbid CSU and PU after 1 year was 21%, as compared to 47% in patients with isolated CU [8].

The lifetime prevalence of PU is estimated to be 4 to 6% [9]. A recent meta-analysis observed that the prevalence of inducible urticaria among patients with CU ranges between 13.1 and 14.9% [10].

The most common form of PU is dermatographism (present in 2 to 5% of the general population and in about 10% of patients with CU), while DPU is observed in up to one third of all CU patients [11]. The frequency of cold urticaria ranges between 5 and 30% of PU [12]. Solar urticaria is rare, with a prevalence of 0.4–0.5% of patients with CU [13]. Heat contact urticaria and vibratory urticaria/angioedema are also rarely observed (0.2 and 0.1% of patients with CU, respectively).

Overview of the Management of Physical Urticarias

The diagnosis of PU is based on the clinical history (data obtained during patient's interrogation and physical examination) and the performance of specific challenge procedures that contribute to confirm the diagnosis, to assess the threshold of the physical stimulus inducing the symptoms, to determine the severity of the disease, to provide avoidance recommendations, and to monitor the response to treatment.

Provocation tests for diagnostic purposes simulate the physical stimulus leading to the formation of wheals and angioedema. Since in rare cases systemic anaphylactic reactions might occur, for example during cold provocation, standard emergency treatment should be available during the performance of those tests.

General measures for the management of patients with PU include the identification and avoidance of the physical trigger and symptomatic pharmacotherapy as recommended by national and international guidelines [1•]. First line therapy includes nonsedating antihistamines in conventional doses, the increase of the dose up to four times if the response is not satisfactory, and alternative medications (omalizumab, cyclosporin A) as an additional resource [14].

For some of the PU, there is the possibility of tolerance induction by means of progressive and controlled long-term exposure to the stimulus [15•]. This approach has been applied to cold urticaria [16, 17], heat urticaria [18], and solar urticaria [19].

Dermographism (Dermatographism, Dermatographia, Dermographic Urticaria, Urticaria Factitia)

This type of PU is characterized by the occurrence of wheals after a pressure or shearing force is applied to the skin. This is the most common form of PU, present in 2 to 5% of the general population. Dermographism may be asymptomatic, although itching can be of enough intensity to oblige the patient to request medical consultation (symptomatic dermatographism). It can be passively transferred [20].

The diagnosis of dermatographism is confirmed by means of stroking the skin with a smooth blunt object such as a wooden spatula or a ball point pen. This test is considered positive if a pruritic palpable wheal is present within 10 min of the provocation. A calibrated dermatographometer is an instrument that applies pressure varying between 20 and 160 g/mm² (196–1569 kPa). The development of a pruritic palpable wheal to applied pressure of <36 g/mm² is considered diagnostic of symptomatic dermatographism. The use of different levels of pressure allows to determine the trigger threshold.

Another simpler tool used to investigate patients with dermatographism is called Fric Test® (Moxie, Berlin, Germany), a plastic comb with four tips (3.0, 3.5, 4.0, and 4.5 mm in length, respectively) which applies graded shearing forces to the skin allowing the determination of the trigger threshold. The instrument is placed vertically and stroked once across the width of the volar surface of the forearm for a distance of approximately 60 mm. The test is considered positive if a pruritic palpable wheal of ≥3 mm width is present within 10 min of provocation (Fig. 1).

The management of dermatographism involves trigger avoidance, and nonsedating second generation H1 antihistamines at approved doses or increased (up to four times) doses. Alternative treatments for nonresponders include omalizumab, cyclosporine, phototherapy, and photochemotherapy [21–25].

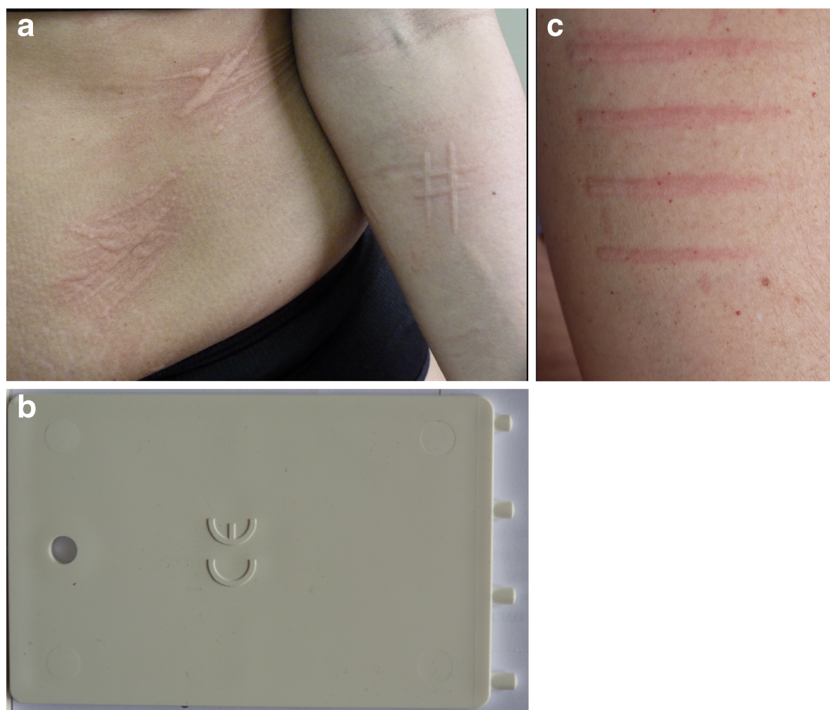
Delayed Pressure Urticaria/Angioedema

Patients with DPU develop wheals or swelling after 4 to 6 h of skin exposure to a sustained pressure stimulus, although in some cases a delay of 12 to 24 h for the appearance of the lesions is observed. Biopsies of the lesions show a mixed infiltrate of neutrophils and eosinophils [26].

The diagnosis of DPU can be confirmed by means of a challenge with 7 kg of weight on a 3-cm shoulder strap suspended over the patient's shoulder for 10 to 15 min. A positive result is the development of urticaria and/or delayed angioedema at the site of pressure after 4–5 h.

Management of DPU includes preventive measures, for example, avoiding static pressures, use of soft shoes, avoidance of tight clothing, use of nonsedating antihistamines (frequently in higher-than-standard doses). Alternative drugs that

Fig. 1 Dermographic urticaria. **a** A 39-year-old female patient with dermatographic urticaria. **b** Fric test® instrument. **c** Positive result of the Fric test



have been employed in nonresponder patients include montelukast [27], omalizumab [28, 29], dapsone [30], sulfasalazine [31], anti-TNF [32], and theophylline [33].

Cold Contact Urticaria (Cold Urticaria, Acquired Cold Urticaria)

Patients affected by cold urticaria are more often young adults that rapidly experience pruritus, erythema, and swelling when the skin is exposed to a cold stimulus (cold air, liquids, or solid objects) (Fig. 2a). These patients are at risk of severe systemic reactions associated with hypotension and fatalities triggered by systemic cold exposure such as immersion into cold water have been reported.

Cold urticaria is classified from the clinical point of view into three types: type I is cold-induced *localized* urticaria and/

or angioedema, type II is *generalized* urticaria, and type III is characterized by *severe systemic* reactions [34].

This condition is mediated by IgE autoantibodies directed to a cold-dependent skin antigen [35], and it can be passively transferred [36].

An additional clinically useful system to classify cold urticaria is into the following: (1) *primary idiopathic* cold urticaria, (2) *systemic* cold urticaria due to infections (HIV, syphilis, hepatitis, parasites, bacterial infections), cryoglobulinemia, autoimmunity, leukocytoclastic vasculitis, cold agglutinin disease, and (3) *atypical and familial syndromes*.

Cold urticaria has to be distinguished from autoinflammatory diseases, where cold-induced wheals are accompanied by recurrent fever, arthralgia, or hearing loss [37], including rare cases of phospholipase C γ -2 gene mutations [38], and mutations in cold-induced autoinflammatory syndrome-1 gene resulting in cryopyrin-associated periodic syndrome (CAPS) [39, 40].

Fig. 2 Cold urticaria. **a** A 14-year-old boy with cold urticaria induced by exposure to cold air during winter season. **b** Positive ice cube test

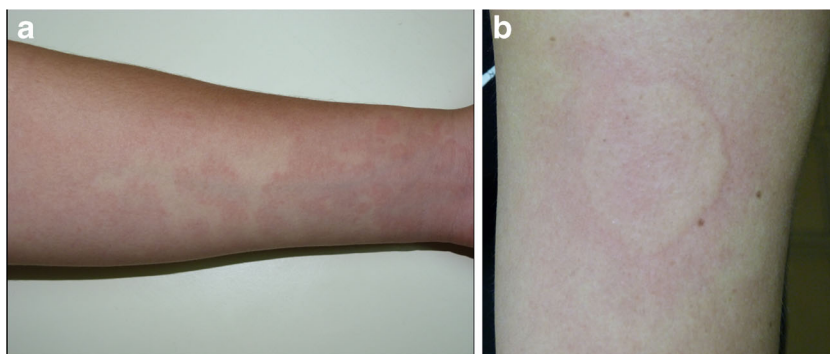




Fig. 3 Solar urticaria. A 66-year-old female patient with solar urticaria. Observe the lesions on sun-exposed areas (“V” of the neck)

Other diagnostic considerations are atypical cold urticarias, including systemic, cold-induced cholinergic urticaria, cold-dependent dermatographism, delayed cold urticaria, and localized cold-reflex urticaria [34], and familial syndromes [41, 42].

The diagnosis of cold urticaria is confirmed by means of the application of a cold stimulus, for example, an ice cube on the forearm skin for 5 min (ice cube test). A positive result consists of a wheal and flare reaction observed during rewarming of the skin to ambient temperature (Fig. 2b).

A Peltier effect-based instrument called Temp Test® (CK Electronic, Köln, Germany) has been also proposed to study patients with cold urticaria. It is useful to establish the highest temperature and/or shortest stimulation time that will induce a wheal-and-flare reaction. The simultaneous application of 12 different temperatures from 4.0 to 42 °C allows the evaluation of the critical temperature threshold (CTT) and the cold

stimulation time threshold (CSTT), which will help to define the severity of the disease [43, 44].

Management of cold urticaria includes the following:

1. Avoidance of cold exposure, cold foods or drinks
2. Pharmacotherapy:
 - Nonsedating antihistamines, in recommended or increased doses [45, 46]
 - Ketotifen
 - Montelukast
 - Omalizumab [22, 47]
 - Antibiotics: doxycycline, penicillin [48]
 - Anakinra and etanercept [49, 50]
3. Induction of tolerance by gradual immersion in cold water at regular intervals [51] As already mentioned, this procedure has the risk of systemic reactions [52]. Also, maintenance of tolerance requires regular cold exposure.

In severe cases, an emergency action plan should be instituted which includes the prescription of epinephrine autoinjectors.

Heat Contact Urticaria (Heat Urticaria)

Heat constitutes an exceptionally rare cause of urticaria where wheals appear after skin contact with a warm object. It has to be differentiated from cholinergic and solar urticaria.

The diagnosis is confirmed by means of the application of a hot stimulus to the skin of the volar forearm (for example, a metal/glass cylinder filled with hot water, or hot water baths up to 44 °C for 5 min with a 10-min observation period). Alternatively, the Temp Test® equipment can be used. The

Fig. 4 Cholinergic urticaria. A 28-year-old patient with cholinergic urticaria. This patient presented urticaria resistant to antihistamines, even at four times the recommended dose, and responded favorably to omalizumab



Table 1 Clinical features of physical urticarias

PU subtype	Clinical picture
Dermographism	Linear wheals from shear force, often localized to sites of pressure by clothing, shoes, underwear, belts. Also sites of trauma, friction, or scratching
Delayed pressure urticaria	Pruritus, swelling, and pain 4–12 h after exposure to pressure
Cold contact urticaria	Wheals, erythema, and itch after exposure/contact with cold air, liquids, or objects
Heat contact urticaria	Reaction limited to area of exposure to heat
Solar urticaria	Immediate reaction consistent of wheals on areas of skin exposed to sunlight (UV and visible light)
Vibratory urticaria	Erythema and swelling at the site of vibratory stimulus

test is positive if the test site shows a palpable wheal and flare-type skin reaction, accompanied by itch or a burning sensation.

Heat urticaria is usually treated with nonsedating H1 antihistamines. There are reports of the use of omalizumab in refractory cases [53, 54].

Solar Urticaria

Patients with solar urticaria develop wheals rapidly after exposure of the skin to sunlight (UVA, 320–400 nm; or visible wavelengths, 400–600 nm) (Fig. 3). Less commonly wheals are induced by UVB, 280–320 nm, or infrared radiation, >600 nm [55].

Solar urticaria is classified into two types: type I occurs in patients who have precursors in the serum, plasma, or cutaneous tissue fluid that become photoallergens once activated by the appropriate wavelength and bind to IgE autoantibodies bound to IgE receptors, resulting in mast cell degranulation and release of histamine and other inflammatory mediators. Type II is also IgE-mediated, but

precursors are found in both, healthy individuals and solar urticaria patients [56].

The diagnosis of solar urticaria is done by phototesting to various wavelengths of light to simulate provocation of the urticarial lesions. Various alternatives are as follows: a slide projector light bulb (for visible light), a fluorescent black light (UVB and UVA wavelengths), a fluorescent sunlamp (UVB and UVA wavelengths), or infrared lamp (infrared wavelengths). The minimal urticarial dose can be determined by exposing a 1-cm² area of skin at a distance of 10 cm from the light source.

Solar urticaria has to be distinguished from the following:

- Polymorphous light eruption: in this condition, lesions usually last longer than 24 h.
- Erythropoietic protoporphyria: in this disease, lesions are painful rather than pruritic, the onset is earlier in life, it is associated with a positive family history, and protoporphyrin levels are elevated.

The treatment of solar urticaria is based on the following:

1. Avoidance of relevant wavelengths and use of protective sunscreens and clothing

Table 2 Diagnostic methods useful to investigate patients with physical urticarias

PU subtype	Diagnostic methods
Dermographism	Stroking the skin with a wooden spatula or ball point pen Fric test® Dermographometer
Delayed pressure urticaria	7 kg weight bearing on shoulder or lower leg for 15–20 min Dermographometer
Cold contact urticaria	Wheal and flare with pruritus from contact with cold object (“ice cube test”) Temptest® Hand immersion in a 10 °C water bath for 5 min
Heat contact urticaria	Hot water (45–50 °C) in glass beaker for 1–10 min
Solar urticaria	Phototesting
Vibratory urticaria	Vibratory stimulation for 1–5 min with vortex

For detailed explanation, see text

2. Pharmacotherapy:

- Nonsedating H1 antihistamines
 - Omalizumab [57–61]
 - Cyclosporin A [62]
 - Intravenous immunoglobulins [63]
 - Afamelanotide, an alpha MSH analog and melanocortin receptor agonist [64]
3. Photochemotherapy with oral 8-methoxypsoralen given before UVA irradiation [65]. This form of treatment carries the risk of skin burns and cancer
 4. Plasmapheresis [66, 67]
 5. Desensitization to induce tolerance by gradually increasing exposure over time [68–70]

Vibratory Urticaria/Angioedema

Patients with vibratory urticaria/angioedema experience pruritus and swelling minutes after the skin is exposed to a vibratory stimulus, for example bores used in dentistry or by building workers. The condition can be familial.

It can be diagnosed by exposure of the skin to a vortex mixer supporting patient's forearm under the wrist and elbow so that the skin of the forearm, hand, or finger rests in the rubber cup of the vortex. Then, the mixer is vibrated at a constant speed between 780 and 1380 rpm for at least 1 min and up to 5 min.

Treatment of vibratory urticaria consists of avoiding provocative stimuli, "warming up" before exercising [71], nonsedating anti-H1 antihistamines, ketotifen [72], and progressive exposure to vibratory stimuli to induce tolerance [73].

Other Inducible Urticarias

As previously mentioned, cholinergic urticaria and aquagenic urticaria are not currently included into the group of PU because in them wheal formation is not induced by a physical stimulus.

Cholinergic urticaria is produced by the elevation or reduction of core body temperature. Lesions appear after exercise or local application of heat. Pinpoint non-follicular lesions measuring 1–3 mm, mainly located on the trunk and upper limbs, are the typical manifestation of this condition (Fig. 4). It is often triggered by exercise, but also by emotional stress, hot and spicy foods or beverages, and it has been postulated that its mechanism of production depends on the presence of an autoantibody to a sweat antigen, since a wheal or flare reaction to autologous diluted serum is present [74].

The diagnosis is confirmed with exercise challenge or passive warming (hot water immersion) and rest. Treatment is similar to other forms of CU, and includes avoiding overheating, nonsedating antihistamines; in some cases a favorable response to omalizumab has been observed [75]. Desensitization to autologous sweat has been also proposed [74].

Aquagenic urticaria is a rare condition triggered by contact with water, regardless of its temperature. It appears as 1–2 mm wheals on the upper part of the body. More frequently it occurs as isolated cases, but familial forms have been reported [76].

The diagnosis is confirmed through the application of a water-drenched compress at 35–37 °C on the skin of the upper body for 20–30 min. It must be differentiated from aquagenic pruritus, cold urticaria, heat urticaria, and cholinergic urticaria. Antihistamines, UV therapy, and barrier creams are usually employed for the treatment of this disease [77–79].

Conclusions

Physical urticarias are frequent types of chronic inducible urticarias that can be debilitating due to a number of limitations imposed to the normal life of the patient. It can be associated with other types of chronic urticaria, and more than one form of PU can be observed in one patient. Physical urticaria is associated with a worse prognosis and duration, further compromising the quality of life of the affected individual. Most frequent subtypes of physical urticaria are dermographism and delayed pressure urticaria. The diagnosis of the different subtypes is established through specific provocation tests (pressure, cold, heat, sunlight, vibration) and the management is similar to the one indicated in other forms of CU, encompassing avoidance measures, pharmacologic therapy with nonsedating antihistamines, and alternative medications in refractory cases.

Table 1 summarizes the clinical features that can lead to the suspicion of PU. Table 2 presents the diagnostic methods recommended for the confirmation of the different forms of PU.

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