

Physical Urticarias and Cholinergic Urticaria

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KEYWORDS

- Physical urticaria • Urticaria factitia • Pressure urticaria • Cold urticaria
- Heat urticaria • Solar urticaria • Vibratory urticaria/angioedema
- Cholinergic urticaria

KEY POINTS

- Physical urticarias and cholinergic urticaria are more frequent, chronic, and debilitating than commonly thought.
- Many patients are severely impaired in their quality of life, but disease-specific instruments to measure this are missing.
- The signs and symptoms of physical urticarias and cholinergic urticaria are known to be mast cell-mediated, but their underlying causes remain to be identified and characterized.
- Trigger threshold measurements are important to inform patients and physicians about disease severity and to monitor its course over time as well as treatment responses.
- As of yet, validated protocols and instruments to measure trigger thresholds are available only for urticaria factitia/symptomatic dermographism, cold contact urticaria, heat contact urticaria and solar urticaria, but not for the other physical urticarias and cholinergic urticaria.
- Treatment choices include trigger avoidance and second-generation nonsedating H1-antihistamines in all physical urticarias and cholinergic urticaria.
- Future research efforts will need to focus on the identification of underlying causes and associated mast cell secretagogues, because this will allow for the development of curative, rather than symptomatic, therapies.

INTRODUCTION

Physical urticarias (PhysU) are characterized by itchy wheal and flare-type skin reactions and/or angioedema induced by external physical factors, which include mechanical (friction, pressure, and vibration), thermal (cold, heat) stimuli, and electromagnetic radiation (solar radiation).¹ Thus, characterized by the nature of the eliciting factor

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acting on the skin, physU encompass several distinct subtypes: urticaria factitia/symptomatic dermographism (UF/SD), delayed pressure urticaria (DPU), vibratory urticaria/angioedema, cold contact urticaria (ColdU), heat contact urticaria (HeatU), and solar urticaria (SolU).² Cholinergic urticaria (CholU), which is also an inducible form of urticaria, is not classified as a PhysU, because its symptoms occur as a response to a rise in body temperature. The signs and symptoms of CholU are typically provoked by exercise or hot showers or baths and not by exogenous physical triggers acting on the skin.² PhysU need to be accurately distinguished from other inducible forms of urticaria as well as from chronic spontaneous urticaria (Table 1).

In CholU and in all PhysU subtypes except for DPU, wheal and flare responses, or angioedema, appear rapidly (ie, within minutes) after exposure to the relevant trigger and they last for a short time (several minutes to hours). However, systemic reactions with generalized urticaria and variable extracutaneous manifestations can also occur.^{3,4} PhysU and CholU are chronic conditions and comprise up to 25% and 5% of cases of chronic urticaria, respectively. They occur most frequently in young adults.^{5–7} Some patients exhibit more than one physical or other subtype of chronic urticaria simultaneously.^{8–10}

The underlying causes of PhysU and CholU remain poorly understood. Pathogenetically, the activation of skin mast cells and their release of histamine and other proinflammatory mediators are the most relevant factors.¹¹ However, it is largely unknown how and why physical stimuli or the increase of body temperature activate skin mast cells.

PhysU and CholU are usually diagnosed from patients' case histories and the results of provocation testing. Patients who are suspected to have more than one PhysU should be tested for every potentially relevant trigger.² Furthermore, measurements of individual trigger thresholds should be done. This allows both patients and physicians to evaluate disease activity and response to the treatment.¹² The treatment of inducible urticarias including PhysU and CholU relies on 2 basic principles: avoidance of eliciting stimuli and inhibition of mast cell mediators, such as histamine. However,

Table 1 Classification of inducible forms of urticaria			
Types of Inducible Urticaria	Type of Stimuli	Subtypes of Inducible Urticaria	Relevant Trigger
Physical Urticarias	Mechanic	Symptomatic dermographism ^a	Friction, rubbing
		DPU	Static pressure
		Vibratory urticaria/angioedema	Vibration
	Thermal	Cold contact urticaria	Cold contact
	Electromagnetic waves	Heat contact urticaria	Heat contact
		Solar urticaria	UV/visible light
Other inducible urticarias	—	Cholinergic urticaria	Increase in body temperature due to exercises, warmth, emotional distress
		Aquagenic urticaria	Water contact
		Contact urticaria	Contact with urticariogenic substances

^a Also called urticaria factitia.

complete avoidance of relevant triggers is often impossible or associated with unbearable impairment of daily activities. Therefore, second-generation nonsedating H1-antihistamines are recommended as a first-line symptomatic treatment.¹³ However, in most patients, higher than standard dosing is required to control the symptoms. In addition, desensitization to triggers is possible and helpful in some PhysU, such as SolU and ColdU and in CholU.

The aim of this review is to discuss the current diagnostic and therapeutic possibilities for each form of PhysU and for CholU.

URTICARIA FACTITIA/SYMPOMATIC DERMOGRAPHISM: THE MOST COMMON PHYSICAL URTICARIAS

UF/SD is the most common form of PhysU (about 50% of PhysU) with an estimated prevalence of up to 5% of the general human population.⁵ In accordance with the word dermographism, which means writing on the skin, the disease is characterized by itching and/or burning skin and strip-shaped wheals due to shear force acting on the skin (eg, by scratching or rubbing; **Fig. 1**).^{1,14} Symptoms typically persist for 1.5 to 2 hours.^{1,15,16} In most patients, symptoms substantially influence everyday life, for instance, the choice of clothes or engaging in physical activity.^{1,17} According to the literature, the average duration of the disease is 6.5 years, with great variance.^{1,15,16} UF/SD is different from other forms of urticarial dermographism including simple dermographism (red dermographic wheal with no itching or axon flare), which affects about 5% of otherwise normal young adults.^{18,19} Cholinergic dermographism, associated with CholU, delayed dermographism, and localized dermographism, which is restricted to the sites of insect bites, tattoo marks, and so on, are rare forms of urticarial dermographism.^{20,21}

Although the disease has been known for many years,²² its cause is largely unknown. Reports in the older literature indicate that, in some patients, the injection of their serum into healthy volunteers induces wheals after scratching.^{19,23,24} Possibly specific immunoglobulin (Ig) E to autoallergens generated by exposing the skin to shear force could play a role in the pathomechanism in some UF/SD patients.

Patients who, based on their history, are suspected to have UF/SD should be subjected to provocation tests, which should include the assessment of their thresholds—the lowest shear force needed for causing wheals. Evaluation of thresholds should be



Fig. 1. Marked symptomatic dermographism with strip-shaped wheals after provocation with FricTest 4.0. Positive reaction for all trigger strengths.

performed initially, as well as during follow-up visits to monitor disease progression and to assess the efficacy of therapy. Skin provocation tests should be done on the volar forearm or the upper back by rubbing of the skin. A wooden spatula or the end of a ballpoint pen can be used. For optimal results, special dermatographometers should be used. One example of such a dermatographometer is FricTest (Moxie GmbH, Berlin, Germany) (**Fig. 2**). This instrument allows for simultaneous testing of 4 different strengths of shear force, which is ideal for threshold testing. Another example is a pen-shaped dermatographic tester with a spring-loaded tip that can be adjusted to exert different strengths of shear force (HTZ Limited, New Addington, Croydon, Surrey, United Kingdom). Both dermatographometers are placed vertically on the skin, and the shear force is caused by their movement across the skin with a predetermined pressure. UF/SD provocation tests are positive when a wheal occurs at the provocation site after 10 minutes.^{2,25}

The aim of treatment in UF/SD and in all other chronic urticarias is the absence of symptoms and could be achieved by avoiding exposure of the skin to rubbing, scratching, and shear force-inducing situations. However, avoidance is difficult, if not impossible, for patients. Symptomatic treatment, therefore, is the therapy of choice and SD/UF patients should receive, as first-line therapy, a nonsedating second-generation H1-antihistamine at standard dose. Some patients will not experience complete protection with this approach, in which case increasing the dose to up to 4 times the standard dose is recommended.^{1,13,14} Third-line treatment options include omalizumab,^{26,27} cyclosporine A,²⁸ and leukotriene antagonists such as montelukast. Ultraviolet (UV) B light therapy has also been reported to be effective.²⁹ However, controlled studies are missing.

DELAYED PRESSURE URTICARIA: THE ONLY PHYSICAL URTICARIAS THAT COMES WITHOUT WHEELS

DPU is characterized by erythematous angioedema-like swellings. These swellings are typically located at skin sites exposed to pressure but can also occur on mucous membranes (eg, of the upper airways and oropharynx). Swellings are induced by vertical pressure and can be associated with itching, burning, or pain. Systemic symptoms such as flulike symptoms, arthralgia, or malaise can occur. Typical situations that elicit swellings in DPU patients are carrying objects (shoulder strap of bags and backpacks), walking in tight shoes, standing (eg, barefoot on a ladder), or prolonged

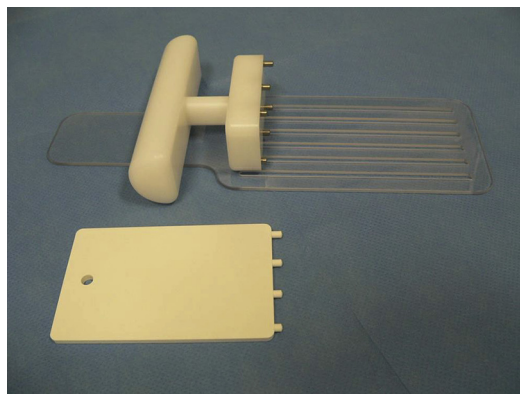


Fig. 2. Special dermatographometers (FricTest 3.0 [top] and 4.0 [bottom]) for skin provocation.

sitting on uncushioned chairs. Typically, swellings occur after exposure to pressure with a delay of 4 to 8 hours and they usually persist for several hours (in some patients more than 24 hours). The average duration of DPU is 6 to 9 years. DPU often impairs quality of life markedly. DPU patients frequently also have chronic spontaneous urticaria and/or other forms of PhysU. Up to one-third of patients with chronic spontaneous urticaria report aggravation of symptoms at skin sites exposed to pressure (belt, bra). In these patients it is important (but sometimes difficult) to clarify whether they have DPU and chronic spontaneous urticaria or if their chronic spontaneous urticaria is exacerbated by pressure. Pressure-induced skin lesions in patients with chronic spontaneous urticaria are usually of shorter duration and more superficial than the angioedema-like swellings in DPU.

For the diagnosis of DPU, different provocation test methods are available: ideally, weighted rods or dermatographometers are used and test readings are done after 30 minutes and after 4, 6, 8, and 24 hours. Tests are positive if a red swelling is palpable 6 hours after provocation.

DPU patients should be educated on the benefits of avoiding exposure to vertical pressure. Recommended drug therapy regimens include second-generation non-sedating H1-antihistamines; however, often higher than standard doses are needed. Other possible treatment options include montelukast, dapson, sulfasalazine, omalizumab, and anti-tumor necrosis factor (TNF).^{1,5,15,16,30,31}

COLD CONTACT URTICARIA

ColdU, also called acquired cold urticaria, is a common subtype of PhysU, characterized by itchy wheal and flare-type skin reactions or angioedema after exposure to cold. Typically, symptoms occur within minutes after cold contact (cold air, cold liquids, or objects) and are restricted to the skin areas exposed to cold. However, extensive cold contact (eg, swimming in cold water) may lead to systemic reactions accompanied by hypotension and loss of consciousness.³ Several cases of death have been reported because of anaphylaxis while swimming in cold water.³² Up to 72% of ColdU patients experience at least one systemic reaction after extensive cold exposure.^{3,32–34} Besides aquatic activities, patients should avoid ice-cold drinks and food to prevent oropharyngeal edema. ColdU may occur at any age but shows a peak in young adults and a weak predominance in women.^{3,33,35} The mean duration of symptoms ranges between 4.8 and 7.9 years.^{3,33,35} Up to one-third of all PhysU cases are ColdU.³⁶

Atypical, rare forms of ColdU are also described.^{36,37} These conditions include delayed ColdU, where localized whealing develops up to 24 hours after cold exposure; cold-dependent dermatographism, which is characterized by the occurrence of urticarial lesions restricted to cold-exposed and mechanically stimulated skin, cold-induced cholinergic urticaria, which is induced by exercising in cold environments, systemic atypical acquired cold urticaria elicited by specific or unique stimuli (eg, cold wind). In contrast to ColdU, atypical forms show negative results in standard cold provocation tests. Some extremely rare hereditary (autosomal-dominant) conditions such as familial delayed cold urticaria, familial cold auto-inflammatory syndrome, and familial atypical cold urticaria also present with cold-induced wheals. Pathogenetically, these hereditary diseases are characterized by an activation of the NLRP3 inflammasome complex due to a mutation of CIAS1/NLRP3 and the release of interleukin-1 β .³⁸ The central role of interleukin-1 β is demonstrated by the exceptionally good response of disease-specific symptoms to interleukin-1 β antagonists.³⁹

In contrast, ColdU signs and symptoms are induced by histamine and other pro-inflammatory mast cell mediators, such as TNF, leukotrienes, prostaglandin D₂, and

platelet-activating factor released in response to cold exposure.^{40–42} The exact mechanism of mast cell activation, however, still remains unknown. In a recent study, 5 of 9 ColdU patients were found to exhibit antibodies against IgE or against high-affinity receptor for IgE.⁴³ It has been hypothesized that autoimmune mechanisms (eg, IgE Antibodies to cold-dependent skin antigens) could be involved in the pathogenesis of ColdU, because it can be adoptively transferred to healthy individuals by intracutaneous injection of the serum of some ColdU patients.⁴⁴

In patients with a history of cold-induced whealing or angioedema, a cold stimulation test should be performed. The traditional method is to place a melting ice cube in a thin plastic bag (to avoid cold damage of the skin) on the volar forearm for 5 minutes. The test response should be assessed 10 minutes after removing the ice cube. It is held to be positive if the test site shows a palpable and clearly visible wheal, which is usually associated with a pruritic or burning sensation.³⁷ A positive ice cube cold stimulation test confirms the diagnosis of ColdU. Patients with a positive reaction to the ice cube test should be evaluated for individual temperature and/or stimulation time thresholds (Fig. 3).² For this purpose, a Peltier element-based electronic provocation device (TempTest, Moxie GmbH) has been developed, which simultaneously tests temperatures from 4°C to 44°C in a standardized and reproducible way (Fig. 4).⁴⁵ Determination of thresholds by TempTest allows both patients and physicians to evaluate disease activity and therapy response.⁴⁶ Laboratory tests are of limited value in most cases of cold urticaria and should be restricted to cases in which the patient's history suggests existence of an underlying disease.⁴⁷

ColdU patients are often severely impaired in their daily lives, especially those with high temperature thresholds who live in countries with a cold climate. Also, ColdU patients are at risk of suffering fatal anaphylactic reactions. Effective therapeutic measures are, therefore, important and needed.³⁷ The underlying causes of ColdU remain unknown, but some patients show remission after antibiotic treatment with doxycycline or penicillin given for several weeks.^{35,48} All patients should be counseled



Fig. 3. ColdU—threshold testing by using TempTest 4.0. Exposure of the skin to temperatures from 4°C to 44°C over 5 minutes. Response assessment 10 minutes after provocation. Cold temperature threshold = highest temperature sufficient to induce a positive reaction, in this case 27°C.



Fig. 4. Peltier element-based electronic provocation device (TempTest 4.0, Moxie GmbH) with temperatures from 4°C to 44°C to confirm cold urticaria and heat urticaria and to determine individual temperature thresholds.

on the importance of avoiding cold, especially patients with higher temperature thresholds. The symptomatic treatment of choice in ColdU is second-generation nonsedating H1-antihistamines. They have been shown to be effective, safe, and well tolerated in several controlled studies and are recommended by the EAACI/GA²LEN/EDF/WAO (European Academy of Allergology and Clinical Immunology/ Global Allergy and Asthma European Network/ European Dermatology Forum/World Allergy Organization) guidelines as first-line therapy.^{13,49} In many patients, however, standard treatment with antihistamines is insufficient. Recent data have shown that the use of high doses of H1-antihistamines is significantly more effective in ColdU than standard doses.^{50–54} Treatment options for antihistamine-resistant ColdU patients include cold desensitization⁵⁵ and omalizumab (anti-IgE) treatment.^{26,56,57} Desensitization, where skin sensitivity to cold is diminished by repeated cold exposure, involves the risk of anaphylactic shock during induction and requires daily cold showers to maintain the protective effect.^{55,58,59} ColdU patients may also benefit from anakinra (anti-interleukin-1) or etanercept (TNF inhibitor) treatment, as shown by recent case reports.^{60,61} However, controlled studies are missing.

HEAT CONTACT URTICARIA

HeatU, also called localized heat urticaria, is a rare PhysU characterized by the appearance of wheal and flare-type skin reaction after heat exposure of the skin. Less than 100 cases of HeatU have been reported in the literature including cases in children and atypical familial localized delayed heat urticaria.¹

As in all other PhysU, skin mast cell activation is held to be critically involved in the pathogenesis, and this is supported by the demonstration of increased plasma histamine levels after exposing HeatU patients to warm water testing.⁶² The relevance of a previously described temperature-activated serum factor remains unknown.⁶³

HeatU wheals are usually well-defined, limited to the area of heat exposure; they typically develop within a few minutes after heat contact and resolve after 1 to 3 hours. Suspicion of HeatU from the case history should be confirmed by local heat testing. Heat should be applied for 5 minutes (metal/glass cylinders, filled with water, hot water bath, TempTest) at a temperature of up to 45°C. Test responses should be assessed 10 minutes after provocation. In patients with a positive response, temperature and/or stimulation time thresholds should be performed.²

Treatment options for HeatU are limited and variably effective. Second-generation nonsedating H1-antihistamines are the first choice for symptomatic therapy.¹³ Some case reports suggest that omalizumab (anti-IgE) may be beneficial in difficult-to-treat patients.^{26,64}

SOLAR URTICARIA

SolU is a rare type of PhysU characterized by urticarial lesions (mostly itchy wheals) that occur immediately (usually within 5–15 minutes) after light (UV and/or visible light) exposure and resolve within less than 24 hours. SolU must be discriminated from the much commoner polymorphic light eruption, which differs from SolU in that sunlight-evoked inflammatory rashes in the former are prolonged and persistent, whereas the wheals in the latter are transitory. A few case reports have reported SolU cases with unusual clinical features such as delayed onset (more than 1 hour), delayed resolution (more than 24 hours), and solar angioedema. A retrospective study from Singapore evaluated 21,974 patients with urticaria over a 10-year period and detected SolU in 0.08% of these patients.⁶⁵ In patients who consult a hospital because of sunlight-related skin problems, the prevalence of SolU was reported to be 2.3%⁶⁶ and 17.8%.⁶⁷ Epidemiologic analyses showed a female preponderance and a peak age onset between 20 and 40 years for both genders, but no influence of the Fitzpatrick skin type on the occurrence or severity of disease.⁶⁶ Atopy is common in SolU patients (up to 48%⁶⁸), and combinations with other PhysU forms are frequent (up to 28%).^{65,69}

UVA is the most frequent action spectrum to elicit skin reactions, followed by visible light and UVB light. Generally, SolU patients have very diverse action spectra. Horio⁷⁰ postulated that this is due to the heterogeneous nature of chromophores or photosensitizers involved as well as ethnic and geographic differences. The results of serum transfer test studies led to the hypothesis of circulating serum factors that cause mast cell degranulation in SolU patients. Based on these studies done in the 1960s and 1970s,^{71–73} distinct subtypes of SolU were postulated, implicating abnormal serum and/or dermal factors. In vitro studies led to the classification of type I SolU (IgE antibodies against an abnormal chromophore) and type II SolU (IgE antibodies against a normal chromophore).⁷⁴ Interestingly, in some cases anti-IgE therapy can completely protect from SolU symptoms⁷⁵ while in others it did not,⁷⁶ which indicates that IgE plays a central role in the pathophysiology of the disease in some but not all patients. Further studies are needed to identify and characterize in detail the pathogenic principles in SolU.

For the diagnosis of SolU, a detailed history and provocation tests are needed. Solar simulators with filters (UVA and UVB) or monochromators (UVA and UVB, visible light) should be used for provocation testing (preferably on the buttocks). UVA should be tested at 6 J/cm² and UVB at 60 mJ/cm². Visible light can also be tested by using a projector (eg, slide projector, 10 cm distance). Positive provocation leads to a rapid urticarial response at the site of exposure within 10 minutes. The test is positive if the test site shows a palpable and clearly visible wheal and flare type skin reaction that is itchy and/or burns.² Threshold testing (minimal urticarial dose) should be performed by varying the radiation dose, which allows the determination of disease activity and response to therapy.⁶⁸

Standard treatment options include avoidance of sunlight, protective clothing, broadband sunscreens, and second-generation nonsedating H1-antihistamines. Unfortunately, exposure to sunlight is hard to avoid, and antihistamines, even at higher than standard doses, provide incomplete protection in most cases. Tolerance can be induced by “light hardening,” usually in rush hardening protocols that required a

hospital setting.^{77,78} Anti-IgE treatment^{26,75} and intravenous immunoglobulin treatment^{79,80} were reported to be effective in some cases, whereas in others these treatments failed.^{76,81} Recently, afamelanotide, an α -MSH α -melanocyte stimulating hormone analogue and melanocortin receptor agonist, was demonstrated to increase melanization and effectively protect from urticarial symptoms in SolU patients.⁸²

VIBRATORY ANGIOEDEMA

Vibratory angioedema (VA) is a very rare PhysU characterized by cutaneous swellings immediately (usually within 10 minutes) after exposure to vibration at contact sites. Single case reports described atypical VA subform (delayed VA⁸³ and hereditary VA⁸⁴). Little is known about its cause. In one case, lesion development was not found to be associated with mast cell degranulation,⁸⁵ whereas in other cases, mast cell degranulation and a raise in histamine levels were detected.^{83,86} VA diagnosis can be confirmed by provocation tests (eg, done with a laboratory vortex mixer).^{16,85} Interestingly, one report demonstrated cutaneous swellings in 35% of the healthy volunteers after provocation testing, which raises the question of the specificity of the test.⁸⁷ Treatment options are limited and consist mainly of avoidance of exposure to vibratory stimulation (eg, use of power tools) and the use of second-generation nonsedating H1-antihistamines.¹⁶ Anti-IgE treatment failed to improve VA in one case report.⁸⁸

CHOLINERGIC URTICARIA

CholU is a very frequent inducible urticaria^{7,89} that is defined by itching and whealing following a rise in body temperature—induced actively (eg, exercise) or passively (eg, hot bath). Angioedema development is very rare.² CholU must be differentiated from exercise-induced urticaria/anaphylaxis, which is induced by exercise but not passive warming and is more often associated with systemic symptoms.

CholU is a disorder of young adults and has a high prevalence in this age group (up to 20%).⁷ In most patients the symptoms get milder with age until they eventually cease to occur completely. It was reported that the severity of the disease shows seasonal changes, with milder symptoms in the summer.⁹⁰ CholU patients typically develop itchy pinpoint-sized short-lived wheals with large flare reactions commonly localized to the limbs and the trunk a few minutes after exercise or passive warming. In some patients, emotional stress or hot and spicy food or beverages can also elicit symptoms. Usually, skin lesions last for 15 to 60 minutes. Atopy⁷ and bronchial hyper-responsiveness⁹¹ seem to be more frequent in CholU patients. Some CholU patients exhibit generalized hypohidrosis.⁹² Japanese studies suggest several distinct CholU subclasses: (1) CholU with poral occlusion, (2) CholU with hypohidrosis, (3) CholU with allergy against sweat, and (4) idiopathic CholU.^{92,93}

There are several reports of cases that suggest that CholU could be caused by poral occlusion, which then leads to the leakage of sweat from sweat glands. Sweat contains numerous enzymes, such as renin-like substances, secretory IgA, IgE, and cytokines, including interleukin 1a and b, and interleukin-8 that, in turn, can induce local inflammation and may cause wheals. Symptoms in CholU patients with poral occlusion reportedly exacerbate in winter and resolve in the summer, suggesting that daily sweating in summer may inhibit the formation of keratotic plugs to prevent the occurrence of CholU.⁹⁴

It is well known that acquired generalized hypohidrosis (AGH) can be accompanied by CholU. A variety of causes, including autoimmunity to sweat glands or to acetylcholine receptors, degeneration of post-ganglionic sympathetic skin nerve fibers, and

poral occlusion (see above) have been proposed as causes of AGH.⁹⁵ CholU in AGH patients may be due to elevated local acetylcholine levels induced by their impaired sweat production. Consequently, excess acetylcholine may activate muscarinic CHRM3 on mast cells in the vicinity of sweat glands to cause wheals.⁹⁶ Acetylcholine is a mast cell degranulator,⁹⁷ and previous reports have demonstrated that subcutaneous injections of cholinergic agents induce sweating and the development of pin-point-sized hives in patients with CholU.

Several recent studies indicate that CholU can be due to an allergy to components of human sweat. Some CholU patients show immediate-type hypersensitivity reactions to their own diluted sweat after intradermal injections, and basophils from these patients react to autologous sweat and release high amounts of histamine *in vitro*.^{98,99} In addition, CholU patients, but not healthy controls, reportedly express IgE to sweat antigens. Very recently, a new allergen component from a fungus was identified in human sweat.¹⁰⁰

To diagnose CholU and to differentiate CholU from exercise-induced urticaria/anaphylaxis, provocation testing should be performed in a 2-step approach. As a first step, moderate physical exercise appropriate to the patients' age and general condition is recommended (eg, on a treadmill or stationary bicycle wearing warm clothing in a warm room). Exercise should be performed to the point of sweating and up to 15 minutes beyond. The test is positive if the typical urticarial rash is seen 10 minutes after exercise challenge. In this case, a passive warming test should be done (at least 24 hours later, 42°C full bath for up to 15 minutes while recording body core temperature to achieve a rise of +1.0°C).² A positive test reaction is seen in CholU, but not exercise-induced urticaria/anaphylaxis patients. These tests are not suited to determine trigger thresholds or to determine and monitor disease activity.

The first-line treatment options in CholU are avoidance of eliciting triggers and second-generation nonsedating H1-antihistamines.¹⁶ Desensitization protocols involving regular physical exercise or treatment with autologous sweat may be useful in some patients,^{101,102} and the same is true for omalizumab,^{26,103,104} scopolamine butylbromide,¹⁰⁵ combinations of propranolol, antihistamines, and montelukast¹⁰⁶ treatments, and injections with botulinumtoxin.¹⁰⁷

SUMMARY

PhysU and CholU are more frequent, chronic, and debilitating than commonly thought. Many patients are severely impaired in their quality of life, but disease-specific instruments to measure this are missing. The signs and symptoms of PhysU and CholU are known to be mast cell-mediated, but their underlying causes remain to be identified and characterized. Trigger threshold measurements are important to inform patients and physicians about disease severity and to monitor its course over time as well as treatment responses. As of yet, validated protocols and instruments to measure trigger thresholds are available only for UF/SD, ColdU, HeatU and SolU, but not for the other PhysU and CholU. Treatment choices include trigger avoidance and second-generation nonsedating H1-antihistamines in all PhysU and CholU. Future research efforts will need to focus on the identification of underlying causes and associated mast cell secretagogues, because this will allow for the development of curative, rather than symptomatic, therapies.

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