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URTICARIA

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2nd Edition

Foreword
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CHAPTER

4

Chronic Inducible Urticaria

Andaç Salman, Ana M Giménez-Arnau

INTRODUCTION

Chronic inducible urticarias (CIndUs) are classified under the chronic urticaria which is defined by the occurrence of wheals, angioedema or both for at least 6 weeks.[1] The occurrence of wheals and/or angioedema in CIndUs requires the presence of a specific trigger. The CIndUs are further divided into physical urticaria and other inducible urticaria depending on the eliciting factors (Table 4.1).[2-4] Although generalized skin lesions or systemic symptoms may occur, the lesions are often localized to the skin in contact to the specific trigger. The CIndUs may coexist with chronic spontaneous urticaria (CSU) or more than one type of CIndU may be present in the same individual.[3] In one series, 36.3% of the patients were reported to have at least one positive provocation test result. The most common forms of CIndUs coexisting with CSU are symptomatic dermographism (SD) and delayed pressure urticaria (DPU).[5]

The diagnosis of CIndUs requires a thorough patient history to identify possible eliciting factors. In any patient with a history suggesting a triggering factor, the standardized provocation tests should be performed.[3]

Table 4.1: Classification and triggering factors of chronic inducible urticarias (CIndUs).

	Synonyms	*Triggering factors*
Physical		
Symptomatic dermographism	Urticaria factitia, dermographic urticaria	Shearing forces on the skin
Cold urticaria	Acquired cold urticaria, cold contact urticaria	Contact cooling of the skin with cool air, liquid or solid objects
Heat urticaria	Heat contact urticaria	Contact heating of the skin
Delayed pressure urticaria	Pressure urticaria	Sustained pressure applied to the skin
Solar urticaria		Exposure to sunlight
Vibratory angioedema		Exposure to vibration
Other CIndUs		
Cholinergic urticaria		Exercise or passive warming
Aquagenic urticaria		Any source of hot or cold water

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CHRONIC INDUCIBLE URTICARIAS DIAGNOSTIC PROVOCATION TESTS AND DISEASE CONTROL

The caution is advised during provocation tests, because in patients with severe CIndUs systemic reactions ranging from dizziness, diarrhea to anaphylactic shock may occur. Experienced and trained physicians in these conditions should perform the provocation tests and emergency treatment equipment should be available.

Discontinuation of the antihistamines (3 days before testing) and glucocorticoids (at least 7 days before testing) and choosing a test site which was not affected for at least 24 hours are recommended to avoid false negative test results.[3]

The provocation testing allows identifying the eliciting factor and determining the trigger thresholds. Threshold assessment is recommended because it is very helpful for the proper counseling of the patients and monitoring the treatment response. The results of the provocation tests should be evaluated 10 minutes after testing except for DPU in which the lesions may develop up to 6 hours after provocation. The details for standardized provocation and threshold testing for CIndUs are provided in Tables 4.2 and 4.3.[3] A recent study have reported a high negative predictive value but a low predictive value of provocation testing in patients with cold, heat and DPU.[6] Therefore in some patients with a highly suggestive history of such CIndUs, the diagnosis cannot be certified with the standardized provocation tests. In those cases, it is

Table 4.2: Provocation tests for chronic inducible urticarias (CIndUs).

CIndU	*Test site*	*Methods*	*Reading time after testing*	*Positive test*
Symptomatic dermographism	Volar forearm or upper back	Moderate stroking with a smooth blunt object, dermographometer (36 g/mm^2), FricTest	10 min	Pruritic wheal
Cold urticaria	Volar forearm	Ice cubes in a plastic bag, cold water baths, TempTest (4–44°C) for 5 min	10 min	Wheal
Heat urticaria	Volar forearm	Metal or glass cylinders filled with hot water, hot water baths, TempTest (44–4°C) for 5 min	10 min	Wheal
Delayed pressure urticaria	Shoulder/ upper back/ thighs/volar forearm	Suspension of weights over shoulder (7 kg, shoulder strap width: 3 cm) for 15 min OR weighted rods (1.5 cm diameter: 2.5 kg; or 6.5 cm diameter: 5 kg) for 15 min. OR dermographometer (100 g/mm^2 for 70 sec)	6 h	Angioedema and erythema
Solar urticaria	Buttocks	UVA 6 J/cm^2 AND UVB 60 mJ/cm^2 and visible light (slide projector)	10 min	Wheal
Vibratory angioedema	Volar forearm	Vortex vibrator for 5 min, at 1,000 rpm	10 min	Angioedema or wheal
Cholinergic urticaria	N/A	Exercise with stationary bike or treadmill (for 30 min, increase pulse rate by 3 BPM) *if positive:* Passive warming with hot baths (42°C bath for 15 min, until body temperature has increased 1°C or more) Pulse-controlled ergometry	Throughout the test and 10 min	Wheals
Aquagenic urticaria	Trunk	A compress or a towel soaked with water at 35–37°C or physiologic saline for 40 min or less	10 min	Wheal

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Table 4.3: Threshold testing for chronic inducible urticarias (CIndUs).[3]

CIndU	*Test site*	*Methods*	*Reading time after testing*	*Threshold*
Symptomatic dermographism	Volar forearm or upper back	Dermographometer, FricTest	10 min	Lowest trigger strength (pin size for FricTest and strength in g/mm^2 for dermographometer) that causes a pruritic wheal
Cold urticaria	Volar forearm	TempTest 4® (4–44°C) for 5 min	10 min	Highest temperature inducing a wheal *Stimulation time threshold (shortest duration of cold exposure to induce a wheal) may also be assessed.
Heat urticaria	Volar forearm	TempTest 4® (44–°C) for 5 min	10 min	Lowest temperature inducing a wheal *Stimulation time threshold (shortest duration of heat exposure to induce a wheal) may also be assessed.
Delayed pressure urticaria	Volar forearm (rods) or upper back (dermographometer)	Weighted rods or dermographometer for 15 min	6 h	Rod with lowest weight (1-2-3-4-5 kg) causing angioedema and erythema
Solar urticaria	Buttocks	UVA/UVB irradiation	10 min	Lowest dose of irradiation (UVA: 2.4, 3.3, 4.2, 5.1, 6 J/cm^2; UVB: 24, 33, 42, 51, 60 mJ/cm^2) causing a wheal response

Source: Adapted from Magerl M, Altrichter S, Borzova E, et al. The definition, diagnostic testing, and management of chronic inducible urticarias—The EAACI/GA^{2}LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71:780-802.

useful to adapt the recommended test to the clinical history of the patients, e.g. in localized cold urticaria (ColdU) or atypical forms of ColdU. The provocation test and the assessment of baseline thresholds help to assess the benefits of the treatment.

Actually the use of the validated patient report outcome urticaria control test (UCT) is recommended to be used in routine clinical practice for assessing the disease control.[7]

BASIS OF CHRONIC INDUCIBLE URTICARIAS MANAGEMENT

Considering the severe impact on quality of life and possible systemic reactions, early diagnosis and treatment are essential. The avoidance of the trigger is the mainstay of treatment and usually very challenging for the most of the patients. In addition to trigger avoidance, symptomatic treatment options include H1 antihistamines, leukotriene receptor antagonists, omalizumab or cyclosporine.[3,8,9] Treatment alternatives including immunomodulatory drugs and desensitization for each type of CIndU is addressed in detail in Table 4.4.

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Table 4.4: Treatment options for chronic inducible urticarias (CIndUs).

	Treatment options		
CIndU	*Level of evidence A*	*Level of evidence B*	*Level of evidence C*
Symptomatic dermographism	H1 antihistamines	Phototherapy Cyclosporine Omalizumab	
Cold urticaria	H1 antihistamines Omalizumab	Desensitization Antibiotics	Cyclosporine Danazol Zafirlukast Etanercept Anakinra
Heat urticaria			H1 antihistamines Omalizumab Desensitization
Delayed pressure urticaria	H1 antihistamines and/or leukotriene antagonists	Omalizumab Sulfasalazine Dapsone Theophylline	Oral coumarins Chloroquine Anti-TNF-alpha Tranexamic acid
Solar urticaria	H1 antihistamines	Omalizumab H1 antihistamines and/or leukotriene antagonists Phototherapy Intravenous immunoglobulins Alpha-MSH hormone analog	Plasmapheresis Cyclosporine
Vibratory angioedema			H1 antihistamines Amitriptyline and bromazepam Ketotifen
Cholinergic urticaria	H1 antihistamines Combination of H1 and H2 antihistamines Danazol	Desensitization with autologous sweat Omalizumab	Methanthelinium bromide Botulinum toxin Surgical ganglion blokage Ketotifen Scopolamine Beta blockers
Aquagenic urticaria			Phototherapy and antihistamines H1 antihistamines Barrier cream

Level of evidence A: double-blinded controlled studies; Level of evidence B: case series or uncontrolled studies with more than 5 patients; Level of evidence C: case reports or small case series.[3]

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CHRONIC INDUCIBLE URTICARIAS PATHOGENESIS

The symptoms of CIndUs are largely caused by the activation and degranulation of mast cells followed by the release of proinflammatory cytokines.[10] Also the efficacy of anti-immunoglubulin (anti-IgE) treatment in various forms of CIndUs suggests a role for IgE in the activation of mast

cells through the FcεIgE receptor.[11] Moreover, increased serum levels of IgE in patients with CIndUs and passive transfer of the disease by transferring the serum of the patients are in support with the role of IgE.[12-14]

In cholinergic urticaria (CholU) increased histamine levels, acetylcholine, sweat allergy, associated serum factors, poral occlusion, hypohidrosis/anhidrosis are suggested to take part in the pathogenesis.[15] In aquagenic urticaria (AU), the research have demonstrated the role of sudden changes in osmotic pressure around the hair follicles[16] and suggest that water-soluble antigens in the epidermis penetrating the skin are responsible of the water-induced erythema and wheals.[17,18] In solar urticaria, the role of skin or serum molecules turning into photoallergens with specific wavelengths has been investigated.[19]

Although various possible eliciting factors, e.g. infections have been proposed for different forms of CIndUs, the exact pathophysiology still remains to be understood.

SYMPTOMATIC DERMOGRAPHISM

Symptomatic dermographism, or urticaria factitia, dermographic urticaria, is the most frequent type of CIndU.[3]

Epidemiology

The frequency of SD is estimated to be 1–5% in the general population.[3] SD usually has a chronic course with a mean duration of disease of approximately 6 years.[8]

Clinical Features

Development of itchy wheals occur due to shearing forces on the skin which may be caused by rubbing, scratching or scrubbing.[3,8] The differential diagnosis includes simple dermographism, which is characterized by the development of erythema or wheals without pruritus.

Diagnosis

The diagnosis of the SD requires a provocation test which can be performed either with a blunt object or instruments such as dermographometer and FricTest[3] (Fig. 4.1).

A smooth blunt object (a pen or a wooden tongue spatula) should be applied perpendicularly to the skin creating a light pressure on the volar forearm or upper back. The test site should be intact and free of any inflammation or infection. The test site should be assessed within 10 minutes of provocation and a pruritic wheal is considered positive. Erythema or just wheal formation without pruritus favors simple dermographism.

Another provocation method for SD is the use of a calibrated dermographometer, which also enables physician to assess the trigger threshold. Symptomatic dermographism is diagnosed if the wheal appears at a pressure less than or equal to 36 g/cm^2.[20] FricTest (MOXIE GmbH, Berlin, *info@moxie-gmbh.de* or *www.moxie-gmbh.de*) is new device validated for the diagnosis of SD. It has four plastic tips with the same diameter of 3 mm and different lengths ranging from 3 mm to 4.5 mm. It is applied perpendicular to the volar forearm skin. Owing to its four tips

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Fig. 4.1: Symptomatic dermographism assessed by dermographometer and FricTest®.
Source: Hospital del Mar, IMIM.

with different lengths, the shearing forces are applied to the skin in a graded manner, thus the trigger threshold can be determined. The development of a pruritic wheal more than or equal to 3 mm width within 10 minutes of provocation is considered positive.[3]

Treatment

Besides trigger avoidance, the first-line treatment for SD is nonsedating second-generation H1 antihistamines.[9] In patients with inadequate symptom control, the H1 antihistamine doses can be increased up to four-fold. The third-line treatment alternative is omalizumab.[21,22] In addition, the use of phototherapy modalities may be of benefit in some patients as the literature data suggests.[3,9,23]

COLD URTICARIA

Cold urticaria, also known as acquired cold urticaria (ACU), cold contact urticaria or urticaria a frigore is characterized by the development of wheals and flare skin type reactions and angioedema after contact cooling of the skin by cold air, liquids or solids[3] (Fig. 4.2).

Epidemiology

It is the second most common type of physical urticaria.[3] It usually affects young adults with a slight female predominance. Its annual incidence is estimated to be 0.05%.[24] In a cohort study 5- and 10-year resolution rates of ColdU were 17.9% and 24.5%, respectively.[25]

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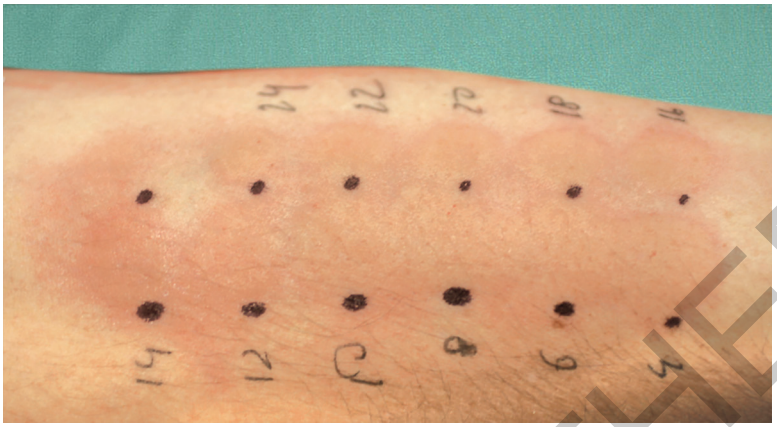

Fig. 4.2: Critical temperature threshold in a patient with severe cold urticaria (ColdU), CTT 24°C.
Source: Hospital del Mar, IMIM.

Clinical Features

The symptoms may occur within minutes following the contact with cold air, liquids or solid objects.[3] Acquired cold urticaria may be idiopathic (primary) or secondary to cryoproteinemia, lymphoproliferative diseases, viral infections including hepatitis B, C and infectious mononucleosis. Thus, the possible underlying causes should be ruled out. The urticarial lesions might be localized, generalized or associated with severe systemic reactions including hypotension and respiratory distress.[3,24,26,27] Up to 19% of patients with ColdU have reported life-threatening reactions. The most common trigger of severe systemic reactions is aquatic activities in cold water. According with Mlynek A et al.[28] the mean temperature capable to induce ACU is 17 ± 6°C (range 4–27°C). Based in a Likert scale we could classify ACU as mild (12.3 ± 8°C), moderate (18.6 ± 7.1°C), and severe (2.0 ± 2.5°C). The patients with severe disease are expected to have longer duration of disease and worse response to treatment with no sedating H1 antihistamines.[24]

The patients with ColdU and a negative provocation test are defined as atypical ACU. An earlier study has reported an increased frequency of systemic reactions in such patients, but the latter studies have failed to demonstrate such relation.[24,26]

Higher rates of atypical ACU along with lower likelihood of achieving a complete symptom resolution was observed in patients with the onset of symptoms during childhood ($p < 0.05$). In patients with atypical ACU, shorter disease duration and lower doses of antihistamines required for achieving disease control were detected ($p < 0.05$). Age at disease onset, symptom severity and ColdU thresholds values were found to be related with longer disease evolution ($p < 0.05$).[19]

Diagnosis

Provocation testing should be performed on the volar forearm skin. Traditional methods include ice cube test and cold water baths.[3] In case of ice cube test, ice cubes in a plastic bag should be used to avoid direct water contact and exclude AU. Critical stimulation time threshold (CsTT) can be assessed by different time exposure to the ice cube. A CsTT less than 3 minutes founded to be

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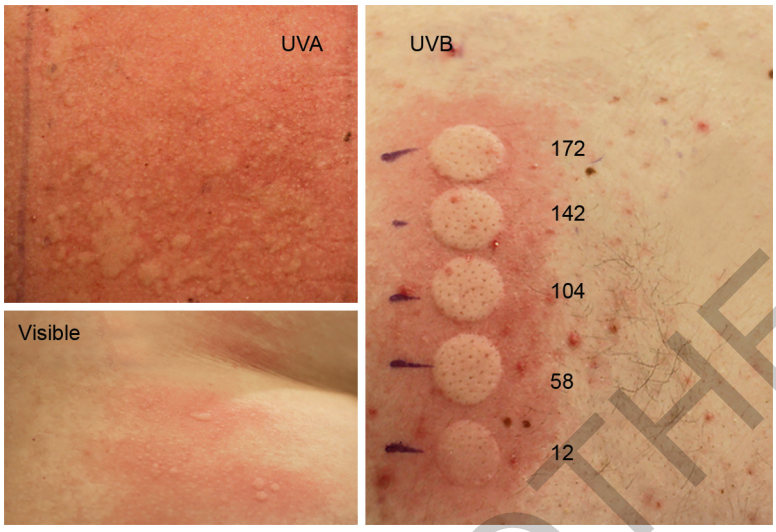

Fig. 4.3: Solar urticaria (SU), induced by ultraviolet A (UVA) and visible light.
Source: Hospital del Mar, IMIM.

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associated with higher disease severity compared with more than 3 minutes.[26] Cold water bath can be used, when the ice cube is negative but caution is warranted as it may induce systemic reactions. Another method for the provocation and trigger threshold test is TempTest4® (Courage and Khazaka, Köln, Germany) which is a Peltier element-based device.[29] It allows performing provocation tests for cold and heat by applying a continuous temperature gradient from 4°C to 44°C. The temperature and stimulation time thresholds can also be determined with TempTest3® (Fig. 4.3). The standardized time for cold provocation testing is 5 minutes. But it can be adjusted to shorter or longer times for patients who are very sensitive or patients with a positive history but without wheals after standard testing, respectively. The test sites should be evaluated 10 minutes after provocation. For patients with a positive provocation test, stimulation time and temperature threshold testing are recommended. The threshold testing are useful for patient counseling, evaluating the disease severity and monitoring the efficacy of treatment.[3,30,31]

Treatment

The first-line treatment for ColdU is nonsedating H1 antihistamines.[3,9,32] However, high doses of H1 antihistamines might be required for symptom control in many patients. Recently, the results of a randomized placebo-controlled study have shown that omalizumab in doses of 150 mg and 300 mg is effective and well-tolerated in patients with ColdU.[33] Other treatment options reported in the literature are cyclosporine, antibiotic treatment (doxycycline or penicillin) and cold desensitization.[34-37] Danazol, anakinra, etanercept, and reslizumab (anti-interleukin-5) have also been reported to be effective in anecdotal reports.[38,39] In addition, prescription of epinephrine autoinjectors for patients who had episodes of cold-induced anaphylaxis and angioedema affecting oropharynx is recommended by some authors.[8,40]

HEAT URTICARIA

Heat urticaria (HU), or heat contact urticaria, is a very rare condition characterized by the occurrence of wheals upon contact with heat.[3]

Epidemiology

It is very rare form of CIndUs.[3] A recent analysis of the published cases revealed 60 patients in the literature. The most of the patients were female and the age of onset of the HU was 34.4 years.[41]

Clinical Features

The wheals develop within minutes of exposure to heat source. Warm baths, hot air and exposure to sun are the most common triggers. Two clinical types of HU were described: (1) immediate HU and (2) delayed HU. Most of the patients had immediate type HU with wheal developing within minutes and resolving within 1–3 hours. On the other hand, in delayed type HU, the wheal/angioedema response occurs 30 minutes to 2 hours after exposure to heat and they resolve within 12–14 hours.[41] In some patients with immediate HU generalized lesions and systemic symptoms including wheezing, syncope episodes may also be seen. Itching is the most frequent symptom in patients with HU although burning sensation was also reported in delayed HU.[41] It should be differentiated from solar urticaria and CholU through the standardized provocation tests.

Diagnosis

Heat provocation testing might be performed using metal/glass cylinders filled with hot water, hot water baths or TempTest4®. Although the standard testing consists of applying heat (at temperatures up to 44ºC) for 5 minutes to the skin of the volar forearm, time and temperature adjustments might be done for some patients. The test site should be evaluated 10 minutes after provocation.[3] Similarly with the ColdU, stimulation time and temperature threshold can be assessed in patients with a positive provocation testing.[23]

Treatment

Because the condition is very rare, the treatment options reported are limited in the literature. Heat desensitization provided a complete response in 60% of the patients. No sedating H1 antihistamines at standard and high doses was effective but full control of symptoms were not common.[41] Omalizumab led to complete remission in three patients.[23,41,42] Colchicine, chloroquine, montelukast, and cyclosporine failed to show any benefit in case reports.[41]

DELAYED PRESSURE URTICARIA

Delayed pressure urticaria is characterized by the development of wheals/angioedema upon sustained pressure applied to the skin.[3]

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Epidemiology

Although the occurrence of DPU as a primary CIndU is rare, its coexistence with CSU is common, affecting between 6.7% and 17% of patients with CSU.[5,43-45]

Clinical Features

The development of the lesions usually takes 6–8 hours (ranging from 30 minutes to 12 hours) and they may persist up to 72 hours. Unlike the other forms of CIndUs, the lesions are associated with burning or pain rather than itching. The clinical differential diagnosis includes SD in which the lesions develop immediately after physical stimulus.[3]

Diagnosis

The provocation testing is done by application of a sustained pressure to the skin. There are several methods including suspension of weights over the shoulder, the application of rods or dermographometer.[20] The weights and rod diameters vary greatly in the literature. The dermographometer is applied for 70 seconds with a pressure of 100 g/mm^2. The test response should be assessed 6 hours after the provocation testing by the physician or the patient.[3,46]

Treatment

The patients with DPU should avoid sustained pressure to the skin such as tight clothing. In addition to standard and higher doses of H1 antihistamines; omalizumab was reported to effective in 3 patients with DPU.[3,9,43] Moreover, dapsone and sulfasalazine have been reported to be effective in large series of patients with DPU.[47,48] Other treatment alternatives are montelukast, colchicine, dapsone, sulfasalazine, escitalopram, anti-TNF, and theophylline.[3,9,49,50]

SOLAR URTICARIA

Solar urticaria (SU) is an idiopathic photodermatosis and a form of CIndU characterized by the development of wheals within minutes following exposure to sunlight.[3,51]

Epidemiology

It is rare condition affecting females more frequently. The mean age of the patients ranged from 29.8 years to 37.9 years in different series.[51,52]

Clinical Features

The urticarial lesions and erythema appear within minutes after exposure to the sun and mostly involve sun-exposed areas. The skin covered with thin clothing may also be affected. Delayed onset of symptoms and systemic anaphylactic reactions were also reported.[51] The most commonly involved action spectrum was visible light followed by ultraviolet A (UVA) and ultraviolet B (UVB).[51,52] The differential diagnosis includes polymorphous light eruption, which is characterized with development of papular, and papulovesicular lesions within hours of sun exposure and persisting up to a few weeks.

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Diagnosis

The diagnosis is made based on history and provocation testing. Discontinuation of the sunscreen and photosensitizing medications before testing is recommended. Solar simulators or monochromator might be used for provocation and the assessment of the minimal urticarial dose (MUD). A slide projector can be used for provocation with visible light. The recommended test site is the buttock and photoprovocation with UVA (6 J/cm^2), UVB (60 mJ/cm^2) and visible light should be performed separately. Urticarial response at the test site within 10 minutes is considered positive. Threshold testing with varying dose of the radiation might be helpful in determining disease severity and response to therapy.[2,3]

Treatment

In addition to strict use of sunscreens, the most frequently used treatment is nonsedating H1 antihistamines.[51] Recently, omalizumab was reported to provide complete clinical remission in patients with SU.[23,53,54] Desensitization, intravenous immunoglobulins, phototherapy modalities, cyclosporine, and afamelanotide have also been reported to be effective.[3,9,51]

VIBRATORY ANGIOEDEMA

Vibratory angioedema (VA) is characterized by an urticarial response to vibration.[3,55]

Epidemiology

Very rare.

Clinical Features

The wheals develop within minutes after exposure to vibration. Atypical forms of VA with delayed onset of lesions or familial forms have also been reported.[56-58]

Diagnosis

The provocation test can be performed using a laboratory vortex mixer. The forearm is held on the vortex mixer that is run between 780 rpm and 1,380 rpm for 5 minutes. The test site is assessed after 10 minutes and the increase of the circumference of the tested arm compared to pretest is considered a positive test.[3]

Treatment

In addition to avoidance of trigger, treatment options are limited to nonsedating H1 antihistamines.[9] Anti-IgE treatment with omalizumab failed to show benefit in one patient.[59]

CHOLINERGIC URTICARIA

Cholinergic urticaria is characterized with pinpoint sized wheal formation triggered by an increase in the core body temperature induced by exercise, emotional stress and hot baths.[3]

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Epidemiology

It affect approximately 4–11.2% of the general population and 20% of the young adults.[3,15]

Clinical Features

The lesions are typically pinpoint sized wheals with surrounding erythema mostly affecting the trunk and extremities. The lesions may sometimes coalesce into larger plaques and usually resolve rapidly within 15–60 minutes.[3] Stinging and tingling sensation are more common than itching. The subjective symptoms usually cause a severe impairment in quality of life and recently the first CholU-specific quality of life instrument has been developed.[15,60]

Recently four subtypes of CholU have been proposed: conventional sweat-allergy type CholU, CholU with palpebral angioedema (CholU-PA), follicular-type CholU with a positive autologous serum skin test (ASST), and CholU with acquired anhidrosis and/or hypohidrosis.[15,61] Conventional sweat-allergy type CholU is caused by sweat allergy and can be diagnosed with a positive autologous sweat skin test (ASwST). CholU-PA is most seen in females and associated with a strong atopic predisposition. ASwST is frequently positive and periorbital angioedema is a distinguishing clinical feature. CholU with acquired anhidrosis and/or hypohidrosis shows a male predominance and always associated with hypo/anhidrosis.[15,62]

Another research has suggested that early-onset CholU (before 36 years of age) is more frequently associated with atopy whereas patients with late-onset CholU are usually female and more likely to have a shorter duration of disease and coexisting other forms of urticaria.[63] The association with atopy is frequent and those with atopic predisposition have more severe CholU.[64]

Severe CholU can even show anaphylaxis[65] but the differential diagnosis includes exercise-induced anaphylaxis which is induced with physical exercise. In contrast to CholU, the lesions are larger and start from the distal parts of the body. The provocation testing with physical exercise is positive, however passive warming test with hot bath is only positive in patients with CholU.[3]

Diagnosis

Provocation testing helps to confirm the diagnosis of CholU and exclude exercise-induced anaphylaxis. An exercise test with a treadmill or stationary bike should be done for 15 minutes or until the onset of symptoms. The typical eruption develops within 10 minutes after testing. A standardized protocol using a pulse-controlled ergometry has also been proposed recently.[3,66] Stop at a final maximum increase of 90 beats/min above the starting level at 30 minutes or at onset of whealing. The onset of sweating and whealing is recorded. In case of a positive exercise test, a passive warming test with hot bath should be performed to rule out exercise-induced anaphylaxis.

Treatment

In CholU with normal sweat function, the first-line treatment is nonsedating H1 antihistamines. In patients with no response updosing of H1 antihistamines, montelukast or omalizumab are recommended.[15] In patients with hypohidrotic CholU, nonsedating H1 antihistamines or in case of severe disease pulse steroid therapy might be of benefit.[15]

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