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Review Article

Chronic inducible urticaria: Clinical presentation, diagnosis, and management

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ABSTRACT

Chronic inducible urticaria (CIndU) is a subtype of chronic urticaria characterized by recurrent itchy wheals and/or angioedema for more than 6 weeks. CIndU has a longer disease duration than chronic spontaneous urticaria (CSU) and wheals are shorter lasting than CSU. CIndU incudes physical and non-physical urticaria. Triggers and diagnosis of subtypes of CIndU differ from each other. Patient education for avoiding triggers is an important aspect of the treatment of CIndU. There is no significant difference in the treatment approach for CIndU and CSU. In this article, we have discussed different types of CIndU, their clinical features, diagnosis, and management.

Keywords: Cold urticaria, Inducible urticaria, Physical urticarial, Solar urticaria, Symptomatic dermographism

INTRODUCTION

Chronic inducible urticaria (CIndU) is a subtype of chronic urticaria characterized by recurrent itchy wheals and/or angioedema for more than 6 weeks. It affects about 0.5% of the general population.[1] Among chronic urticaria, about 5–25% of patients have CIndU and it is most commonly seen in young adults.[2] CIndU has a longer disease duration than chronic spontaneous urticaria (CSU) and wheals are shorter lasting than CSU.[1,3]

CIndU occurs after a person is exposed to some trigger. The subtypes of CIndU include physical and non-physical urticaria [Table 1].[4-6]

CIndU is diagnosed based on the clinical history and confirmed by performing a provocation test.[4]

SYMPTOMATIC DERMOGRAPHISM

Symptomatic dermographism is also known as urticaria factitial or dermographic urticaria. It is the most common type of CIndU. It is characterized by strip-shaped itchy wheals observed on areas that are exposed to rubbing, scratching, and scrubbing. Lesions are itchy and/or burning. Shear force is the trigger for symptomatic dermographism. It may also be provoked after friction with a solid object, right clothes, and bedsheets.[7] Commonly involved body parts include the trunk and extremities. It is diagnosed by clinical history and provocation test, that is, moderately stroking the skin on the volar forearm or upper back of the person using a blunt smooth object such as closed ballpoint pen trop or wooden spatula. Fric test can also be used for its diagnosis. Dermographic tester (36 g/mm^2) is another useful instrument for its elicitation. Provocation testing helps in the confirmation of the diagnosis and also in the assessment of trigger thresholds.[8] Wheals generally appear within seconds to minutes after the application of shear force to the skin. The duration of these wheals ranges from 1.5 to 2 h. Reading is taken after 10 min of testing. The appearance of wheal and itching is considered a positive test.[1,4] Symptomatic dermographism should be differentiated from simple dermographism. The latter is characterized by transient dermographic wheal without itching.[1,2] Recommended laboratory tests in patients with symptomatic dermographism include differential blood count, erythrocyte sedimentation rate, and C-reactive protein.[3] Symptomatic dermographism has a long course, that is, for years.[1,2,4]

CHOLINERGIC URTICARIA

Cholinergic urticaria is characterized by several pinpoint hives, usually ranging from 1 to 3 mm diameter, and having red halos after active (e.g., exercise) or passive body warming (e.g., hot water bath) acts as a trigger for cholinergic urticaria. Sweating, consumption of spicy or hot food, and stress are the other triggers for cholinergic urticaria.[1,4,7,9] It affects about

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Table 1: Subtypes of CIndU.

Physical CIndUs	Non-physical CIndUs
Symptomatic dermographism	Cholinergic urticaria
Cold urticaria	Contact urticaria
Heart urticaria	Aquagenic urticaria
Delayed pressure urticaria	
Solar urticaria	
Vibration urticaria	

4–11.2% of people and is mostly seen during the second or third decade of life. The disease affects both genders; male predominance may be seen.[4,10] Common areas affected include trunk and proximal extremities.[9] Palms, soles, and axillae are not involved. The lesions are associated with stinging or tingling in most cases.[11] The symptoms last for 15–60 min after which they fade on their own.[4,11] Cholinergic urticaria may be seen along with angioedema, atopy, allergic rhinitis, respiratory symptoms, and/or anaphylaxis.[2,11]

The exact cause of the condition is not known; however, histamine, acetyl choline, sweat allergy, serum factors, portal blockade, and anhidrosis may have a role in its development.[11]

It is important to differentiate exercise-induced anaphylaxis from cholinergic urticaria. Provocation testing is useful for differentiating them.

Diagnosis of cholinergic urticaria is done with exercise machines. Patients are advised to exercise on a bicycle trainer or treadmill for 30 min causing an increase in pulse rate of 3/min every minute. The appearance of wheals is considered a positive test. If this test is positive, waiting for over 24 h and performing a passive warming test by 42°C bath are advocated and body temperature is monitored. Bath is continued for 15 min after an increase in body temperature of >1°C from baseline. Reading is taken during the test, immediately after the test, and 10 min after the test. The appearance of wheal is considered a positive test.[1,4]

COLD URTICARIA

Cold urticaria is characterized by the appearance of wheals after contact with cold or cooling air, surfaces, or liquids. The symptoms of cold urticaria include erythema, itching, and wheals or angioedema. It may rarely be associated with anaphylaxis. The condition can cause significant impairment of quality of life and sometimes it can be life-threatening.[12,13]

Cold urticaria can be acquired or have autosomal dominance inheritance. Acquired type is seen at a young age. About 50% of cases show remission or improvement in 5 years.[14] On the contrary, inherited type of disease is often seen in childhood and present throughout life.[15]

The disease is seen in both genders with relatively equal prevalence. The peak incidence of the disease is seen between 18 and 27 years of age. It may prevail in cold climatic countries.[16]

It is diagnosed based on the medical history, clinical symptoms of the patients, and provocation with ice cube testing or Tempest. Melting ice cube in thin plastic bag or Tempest (4°C) applied for 5 min on the patient's volar forearm. Reading is taken 10 min after testing. The appearance of wheels is considered a positive test.[1,4] The recommended laboratory tests include cryoglobulins and infections screening.[1,5] All patients should be counseled about the risks and avoidance of provoking factors.

DELAYED PRESSURE URTICARIA

Delayed pressure urticaria is characterized by cutaneous erythema and edema with often marked subcutaneous swelling following pressure stimulus. The lesions are typically seen 4–6 h after but in some cases may be seen as early as 30 min and last up to 48 h. It differs from other types of inducible urticaria (except vibrational urticaria/angioedema) by the presence of edema of deep dermal layers without wheals.[2,17] It is one of the least common subtypes of CIndU accounting for <5% of cases.[18,19] The disease can last for 6–9 years.[2,20] It is associated with impaired quality of life due to limitations in physical activities and also the impact of selecting clothes or shoes.[21]

Commonly affected body parts include the shoulder, upper back, thighs, or volar forearm. It is diagnosed based on the clinical symptoms, medical history, and provocation test, that is, suspension of weights over the 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 use of a dermographic tester at 100 g/mm^2 for 70 s. Reading is taken for 6 h. The occurrence of erythema or angioedema is considered a positive test.[1,4]

SOLAR URTICARIA

Solar urticaria is a chronic acquired disease associated with photosensitivity and characterized by recurrent episodes of urticaria rash (wheals) seen on skin areas exposed to sunlight. Although not life-threatening, it can significantly impair the quality of life.[22-25] After prolonged exposure to the sun, there may localize angioedema and severe cases may have other systemic symptoms such as weakness, headache, or nausea.

It is also a rare type of chronic urticaria affecting <0.5% of cases of CIndU. Women are commonly affected, without major difference in ethnicity.[26,27] The disease is often seen in people under 35 years of age. Spontaneous resolution may be seen in 15%–25% of patients after 5–10 years of disease duration.[28]

Triggering factors include radiation spectrum from ultraviolet B to visible light (300 nm–500 nm wavelength). Diagnosis is done based on the clinical history and phototesting (UVA, UVB, and visible light sources). Different doses of radiation are delivered to the patients from light

sources kept 10–15 cm from the back. Assessment is done every 10 min for an hour.[1,4]

Patients should avoid direct sun exposure and wear protective clothing, hats, and sunglasses. Sunscreens with a high protection index (SPF 50+) are useful in these patients.[1]

HEAT URTICARIA

Heat urticaria is characterized by the appearance of wheals, itchy erythema after contact with warm air, surfaces, and liquids.[5,29,30] Angioedema may also be seen. Heat urticaria is one of the rarest types of CIndU. Heat urticaria can be localized or generalized.[31] It can be either acquired or autosomal dominant hereditary patterns. Among these, the acquired type represents the most common subtype. Acute symptoms resolve in 1–3 h.[32,33]

Symptoms may be seen after 0.5–2 h after prolonged contact, that is, 12–14 h with a trigger.[30,32] This type is more common in familial cases.[34] Systemic symptoms in the form of weakness, fever, dizziness, head pain, gastrointestinal disturbance, or fever can also be seen.

It is diagnosed based on the clinical history and provocation test with heat source or Tempest (44°C) for 5 min on the volar forearm. Reading is taken 10 min after the test and the appearance of wheal is considered as a positive test.[1,4] Patients should be counseled about the potentially life-threatening problem and educated to avoid known triggers.

AQUAGENIC URTICARIA

Aquagenic urticaria, a very rare form of CIndU, is characterized by small pruritic folliculocentric wheals of 1–3 mm surrounded by 1–3 cm erythematous flare.[4,35] The lesions are associated with itching, burning, and pricking sensations. Body areas commonly affected include the trunk and upper arms. Palms and soles are not involved.[7,35]

The disease starts during puberty and females are more affected.[9,36,37] Water is a triggering factor for this type of inducible urticaria and lesions are seen within 20–30 min after contact with water of any form and any temperature. Sweat and tears can also trigger the occurrence of lesions.[4,35]

Lesions typically disappear within 30–60 min of stopping the contact with water. Aquagenic urticaria should be distinguished from cholinergic urticaria, aquagenic pruritus, cold urticaria, and heat urticaria.[4,11,34,35] Provocation test is useful for this differentiation. A compress or a towel soaked with 35–37°C water or physiological saline is placed on the trunk and taken off after 40 min or earlier after pruritus and wheals are seen at the test site. The test is considered positive if urticarial lesions are seen at the site of contact within 10 min after taking off the compress/towel.[1,4]

VIBRATORY URTICARIA/ANGIOEDEMA

Vibratory urticaria/angioedema is another rare form of CIndU associated with itching/burning and erythematous swelling at the site of vibration.[4,38,39] It can be triggered by jogging, running, motorcycle, bicycle or horse riding, massaging, or working with vibratory machinery.[40] The lesions appear within a few minutes of the trigger and fade within 24 h. Delayed reaction, that is, peaking in 4–6 h and associated anaphylaxis is also possible. Vibratory angioedema can be acquired (more common) or hereditary (less common). People involved in occupations with vibrating machinery are at more risk of developing this type of urticaria.[7,39] It is diagnosed by holding forearm of the patient on a flat plate laid on the vortex vibrator running 1000 rpm for 5 min. Reading is taken 10 min after the test. Appearance of angioedema or wheal is considered as positive test.[1,4]

CONTACT URTICARIA

Contact urticaria is a condition characterized by the appearance of wheal and flare on skin or mucosa within minutes after contact with triggering agent. The lesions disappear within 24 h.[39,41] It can either immunologic, non-immunologic, or indeterminate type.[4,41]

Immunogenic type is an allergic type I IgE-mediated hypersensitivity reaction seen after the previous sensitization.[41,42] The lesions can spread to become generalized urticaria. Subsequently, systemic symptoms and anaphylactic shock can also occur. This step-wise progression is known as contact urticaria syndrome.[41-43] Latex is the common triggering agent, but others such as plant-derived proteins, animal products, enzymes, and drugs/cosmetics/chemicals may also be responsible.[4,42,43]

Non-immunogenic type contact urticaria is seen without prior sensitization. Lesions can be seen at first contact within 45 min up to an hour and only affect areas of contact.[4,41] Triggers include cinnamal, sorbic acid, benzoic acid aldehyde and nicotinic acid esters, plants, or animals (e.g., jelly fish).[4,42] Face and back are more affected than palms and soles. As prostaglandins and leukotrienes are mediators of this disease, response to nonsteroidal anti-inflammatory drugs is seen.[41]

Indeterminate type of contact urticaria can be of mixed type. Exact pathophysiology is of this urticaria is not known. Ammonium persulfate in hair bleaching products is one example of trigger for indeterminate type of urticaria.[41]

It is diagnosed using open controlled application testing, skin prick test, or closed patch tests for 20 min.[1,4]

Antihistamines should be stopped at least 3 days before testing and glucocorticoids for 7 days before testing all types of inducible urticaria.

TREATMENT OF CINDU

Avoidance of the triggers or physical stimuli is very important and should be considered in cases. However, it may not always be possible. Pharmacological therapy

is required to achieve complete symptom control. There is no difference in the recommended treatment approach for patients with CIndU from that of CSU.[5,44] The second-generation H1-antihistamines are the first-line treatment of CIndU. In patients not responding to standard doses, dose of the second-generation antihistamine can be increased up to 4-fold. About half of the CIndU patients do not respond to second generation H1 antihistamines. The third-line treatment for CIndU is omalizumab.[5,6,45] At present, omalizumab is used off-label due to the absence of well-designed clinical trials assessing its efficacy in CIndUs[36,45] and regulatory approvals.

Few placebo-controlled trials are available, but real-life studies and case series have shown efficacy of omalizumab in CIndUs.[37,44-47] Individualized treatments options specific to the subtypes of CIndU are necessary. Disease activity should be evaluated before and during treatment. Threshold testing should be done in all possible cases. Patient-reported outcome measures help to estimate disease activity. Dermatology life quality index and urticaria control test can be used for evaluating quality of life and treatment response, if threshold testing is not available.[5,37,40,48] Disease-specific activity score (Chol-UAS) and QoL questionnaire (Chol-QoL) are specific tools for CholU. ColdU-QoL and SD-QoL are under development.[1,3,49]

CONCLUSION

CIndU represent a variety of chronic urticaria subtypes where as a clinician we need to be aware of the clinical clues. These clinical clues might be first catched by asking the patient 'Can you make the wheals come?' and if there is a certain triggering factor then it would be possible to make a provocation testing with the offending triggering factor and make the diagnosis of this particular inducible urticaria subtype. Other clues are the short duration of the wheals and younger age of the patients. Management of CIndU is based on two steps: avoidance from the trigger or pharmacological treatment. Whereas avoidance is almost impossible, pharmacological treatment is the most feasible approach which consists of using second generation antihistamines and off-label use of omalizumab in antihistamine refractory cases.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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