How to Approach Chronic Inducible Urticaria

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Learning objectives:

1. To describe new insights into the pathomechanisms of chronic inducible urticaria (CIndU).

2. To describe the currently available tools for provocation and threshold testing of the different CIndUs.

3. To recognize the therapeutic and prophylactic options in different CIndUs.

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Chronic inducible urticaria (CIndU) is a group of chronic urticarias characterized by the appearance of recurrent wheals, recurrent angioedema or both, as a response to specific triggers. CIndU includes both physical (symptomatic dermographism, cold and heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory urticaria) and nonphysical urticarias (cholinergic urticaria, contact and aquagenic urticaria). Here, we review the different forms of CIndU with an emphasis on symptomatic dermographism, cold urticaria, cholinergic urticaria, and delayed pressure urticaria. We discuss the clinical features, the diagnostic workup including provocation and threshold testing, and available treatment options. © **2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1119-30)**

Key words: *Chronic inducible urticaria; Cold urticaria; Symptomatic dermographism; Cholinergic urticaria; TempTest*

Chronic inducible urticaria (CIndU) is a subgroup of chronic urticaria (CU) where recurrent pruritic wheals and/or angioedema occur after exposure to specific stimuli. CIndU includes both physical (symptomatic dermographism [SD], cold and heat urticaria, delayed pressure urticaria [DPU], solar urticaria, and vibratory urticaria) and nonphysical urticarias (cholinergic urticaria [CholU], contact and aquagenic urticaria; Table I). CIndU is common, with an estimated prevalence of 0.5%, and many patients are severely disabled, mainly due to the impact of trigger avoidance. In adults, there is a female predominance for the total group of physical urticarias (74% female).[1,2]

CIndU has several differences compared with chronic spontaneous urticaria (CSU). The duration of CIndU is often longer

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Abbreviations used
CholU- Cholinergic urticaria
CIndU- Chronic inducible urticaria
ColdU- Cold urticaria
CSU- Chronic spontaneous urticaria
CU- Chronic urticaria
DPU- Delayed pressure urticaria
FACU- Familial atypical cold urticaria
FCAS- Familial cold autoinflammatory syndrome
PLAID- Phospholipase C-γ2-associated deficiency and immune dysregulation
QoL- Quality of life
SD- Symptomatic dermographism
TRP- Transient receptor potential

than CSU, with lower rates of remission at 1 year and some studies showing the lowest rate of remission after 10 years for cold urticaria (ColdU).[3,4] The duration of individual wheals is often relatively brief for CIndU, lasting minutes to hours, with the exception being DPU. In addition, systemic symptoms of mast cell activation may occur in many types of CIndU. A large portion of patients with ColdU and CholU (35% to 70%) experience systemic reactions including anaphylaxis, after extensive cold exposure and exercise, respectively.[5-7]

CIndUs are diagnosed based on the patient history and the results of provocation tests, which make use of the relevant stimuli in controlled settings. ColdU, for example, is confirmed by applying cold (eg, an ice cube) to the skin of patients, SD is tested by scratching of the skin, and exercise and passive warming (eg, a warm bath) are used for CholU provocation testing. Disease activity, in patients with CIndU, is assessed by threshold testing and activity scores, where available.

The therapeutic goal of CIndU management is to achieve complete symptom control, by trigger avoidance, desensitization, blocking the effects of mast cell mediators (eg, by nonsedating, second-generation antihistamines), and prevention of mast cell degranulation.

PATHOPHYSIOLOGY OF CIndU

The exact pathological mechanisms that result in CIndU are still under investigation. The activation and degranulation of tissue-resident mast cells and the subsequent release of proinflammatory mediators such as histamine play key roles.[8-11] The efficacy of anti-IgE (omalizumab) in many patients with CIndU points to a possible role of IgE in the degranulation of mast cells in CIndU. Type I autoimmunity, also known as autoallergy, is held by many to be of major importance in the pathogenesis of CIndU. The hypothesis is that different autoantigens bind to IgE on skin mast cells and basophils activating these cells.[12] Relevant environmental triggers are thought to induce *de novo* expression of these autoallergens. The autoallergens then bind to IgE (specific for these autoallergens) bound to $Fc_{\varepsilon}RI$ on skin mast cells, inducing their degranulation.[12-14] In support of this concept, patients with CIndU express increased serum levels of total IgE.[13] In several subtypes of CIndU, for example, SD, ColdU, and solar urticaria, the disease is passively transferable by transfer of serum, with IgE being the suggested transferable serum factor.[15,16] In solar urticaria, specific photo-induced autoantigens have been suggested to bind to IgE on mast cells.[17,18] An older study in ColdU showed desensitization by depletion of a cold-dependent skin antigen that can activate mast cells.[19] These studies support the concept that IgE binding to $Fc_{\varepsilon}RI$ on skin mast cells may be important in the pathogenesis of CIndU, explaining the responsiveness of CIndU to anti-IgE treatment.[20-22]

Mast cells and basophils may also be activated through IgE-independent pathways. An area of recent research in physical urticaria has been the role of transient receptor potential (TRP) channels that can be regulated by changes in temperature, pH, or osmolality and produce calcium influx into the cells. Studies using a rat basophilic leukemia cell line suggested that the transient receptor potential cation channel subfamily M member 8 (TRPM8) channel was activated on exposure to cold temperatures with mediator release.[23] However, subsequent studies of human mast cells found no expression of TRPM8 or functional mutations in TRPM8 in patients with ColdU.[24] The role of other TRP proteins in CIndU is unknown.

It has been reported that CIndU and CSU are associated in some patients, especially in physical urticaria and have a worse prognosis. Exact data are not available on the prevalence of CIndU and CSU.[25,26]

Our following review is focused on the 4 most frequent types of CIndU: SD, ColdU, CholU, and DPU.

SYMPTOMATIC DERMOGRAPHISM

Clinical features

SD (synonym: urticaria factitia, dermographic urticaria) is the most common physical urticaria and characterized by itching and/or burning skin sensations and the development of itchy wheals in response to rubbing, scratching, and/or scrubbing, that is, shearing forces acting on the skin. In very rare cases, angioedema can develop. SD is clinically distinct from the more common "simple" dermographism, where whealing, but no itch sensation, occurs after firm stroking of the skin. White dermographism (as seen in atopic patients) is not related to SD.

SD is often linked to CSU. In a group of 245 patients with CSU, SD was the most common type of CIndU, affecting 25% of the CSU group.[26] In a retrospective study of 1200 patients with CSU, SD was the most prominent form of CIndU.[1]

SD is chronic and usually of duration of several years before spontaneous remission. In a questionnaire survey of 91 patients with SD, the mean duration of disease was $6^{1}/_{4}$ years.[27-29] In most patients, the condition was continuous, and 25% had prolonged symptom-free phases.

The symptom severity of SD was evaluated in 150 patients and found to be mild in 17%, moderate in 45%, severe in 33%, and very severe in 6% of patients.[2] Quality of life (QoL) was significantly impaired in 42% of patients, and 7% stated that a normal life was not possible for them. These patients reported being affected with fatigue (62%), sleep disturbance (53%), both during work (60%), or leisure (61%).[2] In 27 patients with SD, 43% reported that their disease had an impact on their QoL. One in 3 patients report that psychosocial stress amplifies the symptoms.[30]

Diagnostic workup

Many patients with SD can be identified through the history. Patients with CU who report pruritus without visible rash, followed by linear wheals that last minutes, should be evaluated for SD. Many patients describe chronic itch or a "skin crawling" sensation leading to scratching. A review of patient photographs for linear wheals can also assist in the diagnosis.