Original Article

Prevalence of Inducible Urticaria in Patients with Chronic Spontaneous Urticaria: Associated Risk Factors

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What is already known about this topic? Chronic urticaria significantly affects patients' quality of life. The identification of possible physical triggers could obviate lifestyle restrictions and improve clinical control.

What does this article add to our knowledge? Environmental factors such as geographical characteristics could play a role in the development of some types of inducible urticaria, whereas atopy and self-reactivity are major risk factors for spontaneous urticaria.

How does this study impact current management guidelines? Most patients avoid physical stimuli that might be triggers of urticaria. Physical triggers must be verified by challenge tests to avoid unnecessary lifestyle restrictions.

BACKGROUND: Information on the prevalence of inducible urticaria (IU) in patients with chronic spontaneous urticaria (CSU) and the factors affecting this prevalence is scarce in the literature.
OBJECTIVES: To estimate the frequency of IU in patients with CSU and to explore possible factors associated with CSU.
METHODS: Patients older than 12 years diagnosed with CSU and a control group with no history of urticaria were recruited from 2 different cities. All patients were questioned about triggers associated with exacerbation of urticaria, and challenge tests were performed for symptomatic dermographism, pressure, cold, water, and exercise. Atopy to mites and self-reactivity to autologous serum were evaluated using skin tests.
RESULTS: The study population comprised 245 patients with CSU and 127 controls. Of the patients with CSU, 186 (75.9%) reported a physical trigger, although only 89 (36.3%) had a positive challenge test result. The challenge tests showed that symptomatic dermographism was the most common type of IU, affecting 24.8% of the CSU group, followed by cold, which affected 13.4%. In the control group, 3.9% of patients were positive for symptomatic dermographism. People living in Medellín city had a higher frequency of symptomatic dermographism 28.5% (odds ratio, 2.1; 95% CI, 1-4.4; $P = .03$) and cold urticaria 16.5% (odds ratio, 3.3; 95% CI, 1.125-9.8; $P = .02$) than did people living in Bogotá (dermographism 14.4% and cold 5.2%). Atopy and self-reactivity were more frequent in patients with CSU than in the control group.
CONCLUSIONS: Physical triggers must be verified by challenge tests to avoid unnecessary lifestyle restrictions. Environmental factors such as geographical characteristics could play a key role in the development of some types of IU, whereas atopy and self-reactivity are major risk factors for CSU. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:464-70)**

Key words: *Atopy; Self-reactivity; Cold; Exercise; Friction; Dermographism; Pressure; Water; Urticaria*

Urticaria comprises a heterogeneous group of diseases that are common in the general population[1] and have a major impact on quality of life. Chronic urticaria (hives and/or angioedema for more than 6 weeks) is estimated to affect between 0.5% and 5% of the general population.[2,3] Chronic spontaneous urticaria (CSU) and inducible urticaria (IU) are the most common types of chronic urticaria and may occur simultaneously or independently. CSU occurs spontaneously with no apparent trigger. IU occurs when the formation of hives is reproducible after a specific stimulus, for example, a mechanical stimulus (friction, pressure, and vibration), thermal stimulus (cold, heat), aquagenic stimulus (water), and electromagnetic stimulus (solar radiation).[4] In a recent meta-analysis,[5] the prevalence of IU was estimated at 13.1% to 14.9% among patients with chronic urticaria. This prevalence is low compared with that reported from other

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Abbreviations used
CSU- Chronic spontaneous urticaria
IU- Inducible urticaria

studies,[6,7] suggesting that results must be interpreted by taking into consideration the methodology used (self-reporting or challenge testing). Outcome can be affected by various factors. The clinical relevance of physical triggers is very important, especially in patients with CSU, where hives and angioedema can occur even without exposure to an inducible stimulus; therefore, mistakes in the identification of triggers lead to unnecessary restrictions that significantly affect quality of life.

Several conditions, including autoimmune diseases and systemic infections and specific drugs, have been associated with urticaria exacerbations. In some cases, the chronicity of the disease could be explained by molecular mimicry; however, to our knowledge, no data have been reported on environmental conditions (eg, temperature and humidity) that affect the onset and prevalence of IU. In addition, information about the role of atopy and self-reactivity in the development of chronic urticaria is controversial.

In this study, we evaluated the frequency of IU in patients diagnosed with CSU on the basis of self-reporting and challenge testing with 5 physical triggers. We also evaluated whether environmental and immunological factors could act as potential risk factors for IU and CSU.

METHODS

Study population

We performed a multicenter, prospective, descriptive study from August 2013 to December 2014. The study population came from a previously formed cohort (URTICA: Urticaria Research of Tropical Impact and Control Assessment, ClinicalTrials.gov number: NCT01940393).[8] Because the aim of the study was to evaluate whether inhibition of the skin test wheal correlated with the clinical effect of antihistamines, patients with baseline inhibition of the cutaneous response to histamine (wheal <3 mm) were not included. The CSU group included patients older than 12 years with chronic urticaria, which was defined as the recurrence of hives, with or without angioedema, on more than 3 days per week and persisting for at least 6 weeks. The disease was diagnosed by an allergist or dermatologist. The exclusion criteria included the following: systemic disease that could explain the hives; systemic corticosteroids during the 3 weeks before recruitment; immune deficiency, dermatitis, and/or any other disease that could alter the results of the skin test; and compromised immune system because of the risk of secondary acute urticaria by infection. We also excluded pregnant women, patients with physical or mental disabilities, people with decompensated cardiovascular disease, and people with a chronic disease that could compromise the patient during challenge testing.

The control group consisted of people older than 12 years with no history of chronic urticaria or history of acute urticaria in the previous 2 years. The control group was evaluated by a physician before enrollment.

We used the *Dermatology Life Quality Index* (DLQI) because it had previously been validated in Colombia. We also used the *Urticaria Activity Score* (UAS) to measure disease severity.

Demographic characteristics

Patients and controls were recruited from 2 cities in Colombia (Bogotá and Medellín) with different environmental characteristics. The genetic background of both populations is very similar and results from a racial admixture between native Americans, Spaniards, and (albeit less frequently) Africans (<10.9%).[9,10] The environmental characteristics of the cities are different: Medellín is located in the Aburra Valley area (6° 14′ 41″ North, 75° 34′ 29″ West), 1479 meters above sea level, with an average annual temperature of 22°C and relative humidity of 66%. Bogotá (4° 35′ 56″ North, 74° 04′ 51″ West) is located 2640 meters above sea level, with an average annual temperature of 14°C and relative humidity of 76%.

Allergen skin test and autologous serum and plasma skin test

IgE sensitization was evaluated using the prick test according to international guidelines[11] with extracts for *Blomia tropicalis*, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*, which are the principal allergens in this region.[12-14] We also evaluated sensitization to foods that the patient associated with exacerbation. Patients with atopy for environmental or dietary allergens received recommendations on avoidance.

Self-reactivity was evaluated using the autologous serum skin test and autologous plasma skin test according to international guidelines. Briefly, 0.05 mL of serum and 0.05 mL of plasma were injected intradermally. Histamine was used as a positive control and saline solution as a negative control. A wheal of 1.5 mm over the negative control after 30 minutes was considered a positive result.[15] European and international guidelines recommend serum over plasma[15]; however, we performed both tests with the same methodology to compare results.

Study design and challenge test

The study design is presented in Figure 1. All participants underwent a complete physical examination before their challenge tests, and the triggers identified by patients were recorded in their clinical history. The physicians performing the challenge test were familiar with the patients' clinical history. In all patients, challenge tests were performed for the 5 most common triggers (dermographism, cold, exercise, water, and pressure). Challenge tests were completed under similar environmental conditions. Patients were acclimated to the challenge room temperature for at least 30 minutes before testing. At least 1 week before the challenge tests, all the patients refrained from taking antihistamines or any other drug that could affect the outcome of the challenge tests. Once the challenge tests were complete, all the participants remained under observation for a period of 2 hours or more depending on the challenge test performed. When patients were discharged, they were advised to photograph any late reactions and/or to visit their health center. The test result was considered positive when hives or angioedema with onset of itching appeared on the area of skin exposed. The protocols used for challenge tests were based on those proposed by international guidelines for IU with some modifications,[2,16] as follows.

Ice cube test. The test was performed by inserting an ice cube in a plastic bag and applying it against the skin of the anterior surface of the forearm for at least 5 minutes and then observing the area for around 10 minutes. In the case of a positive result, the exposure time was reduced by 1-minute intervals to find the threshold at which the reaction was triggered. In the case of a negative result, the test was repeated by increasing the time up to 10 minutes. Each exposure was at a different skin site.