Original Article

Chronic Idiopathic Urticaria: Systemic Complaints and Their Relationship with Disease and Immune Measures

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What is already known about this topic? Patients with chronic idiopathic urticaria can sometimes report systemic symptoms.

What does this article add to our knowledge? Most patients with chronic idiopathic urticaria have systemic complaints with concomitant hives. This subset of patients has greater disease burden and serum tryptase levels.

How does this study impact current management guidelines? Patients with chronic idiopathic urticaria with systemic complaints may require more effective treatment to reduce disease burden.

BACKGROUND: Patients with chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria sometimes report systemic complaints (SCs).
OBJECTIVE: We sought to determine the frequency and characteristics of SCs among patients with CIU, as well as the association of SCs with disease measures, basophil histamine release, and serum tryptase.
METHODS: Adult patients with CIU were recruited from a university allergy clinic. Patients completed a disease symptom survey and underwent blood sampling for subsequent basophil histamine release and serum tryptase measurement.
RESULTS: A total of 155 patients with CIU were surveyed, with 103 reporting SCs with concomitant hives as follows: joint pain or swelling (55.3%), headache/fatigue (47.6%), flushing (42.7%), wheezing (30.1%), gastrointestinal complaints (26.2%), and palpitations (9.7%). Patients with SCs (CIU-SC) were compared with those with no SCs (CIU-NSC). Both groups had similar demographic characteristics (average age in 40s, majority female and white) and basophil histamine release profiles. CIU-SC had significantly greater disease duration (51.5% CIU-SC vs 30.8% CIU-NSC had >4 years duration), emergency department visits (41.7% vs 23.1% had >1 visit in the last year), CIU-related work absences (65% vs 27.5% had >1 day), oral corticosteroid use (84.5% vs 59.6%), quality-of-life impairment (76.1 vs 59.2 SkinDex score), and serum tryptase levels (5.1 ng/mL vs 3.9 ng/mL).
CONCLUSIONS: Despite similar demographic characteristics and basophil profiles as patients with CIU-NSC, patients with CIU-SC have features of greater disease burden (work absences, emergency department visits, and corticosteroid use), quality-of-life impairment, and baseline serum tryptase levels. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Chronic idiopathic urticaria; Chronic spontaneous urticaria; Systemic complaints; Tryptase; Histamine; Quality of life*

Urticaria is characterized by pruritic wheals, with or without angioedema, that generally resolve within 24 hours. It is considered chronic if the disease course lasts 6 weeks or longer. An estimated 80% to 90% of patients with chronic urticaria have no identifiable cause of the disease.[1] It has been observed that some patients with chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria, have associated systemic complaints (SCs) during active wheal flares. These include gastrointestinal symptoms, flushing, joint pain or swelling, cardiovascular manifestations, respiratory symptoms, and other constitutional complaints.[2] Of note, similar symptoms are also reported by patients with mast cell activation disorders, and CIU is noted as one of the conditions that can be a mimicker.[3] Elevated serum total tryptase level has also been demonstrated in patients with CIU relative to healthy controls.[4-6]

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Conflicts of interest: L. B. Schwartz has received travel support from the National Institutes of Health; has received consultancy fees from SanofiAventis, Dyax, ViroPharma, and HELIX; has received research support from CSL Behring, Dyax/Shire, and Merck; shared royalties with VCU Tech Transfer, which received them from ThermoFisher for the tryptase assay; and has received payment to participate in the Atopic Dermatitis in America study from Asthma and Allergy Foundation of America. S. S. Saini has received consultancy fees from AstraZeneca and Teva and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication August 18, 2016; revised November 3, 2016; accepted for publication November 22, 2016.
Available online ■■
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.11.037

Abbreviations used
CIU- Chronic idiopathic urticaria
HR- Histamine release
NSC- No systemic complaints
QOL- Quality of life
SCs- Systemic complaints

In addition to mast cells, basophils have previously been shown to have altered function in patients with CIU.[7] We have demonstrated that patients with CIU can be divided on the basis of functional response of basophils to anti-IgE antibody stimulation into responders and nonresponders.[7] Responders exhibit 10% or greater histamine release, whereas nonresponders exhibit less than 10% histamine release.

At present, there are few studies characterizing the type and frequency of SCs in patients with CIU. There are also limited data on basophil histamine release and tryptase level in this subset of patients with CIU. The aim of this study was 3-fold. First, we examined the frequency and characteristics of SCs among patients with CIU.[8] Second, we determined the association of SCs with other CIU disease severity measures. Last, we examined the relationship between SCs and biomeasures of the disease, including basophil histamine release profile and serum tryptase levels.

METHODS

Study subjects

Adults (≥18 years old) diagnosed with CIU were recruited at the Johns Hopkins Asthma and Allergy Center, a tertiary care referral center. Inclusion criteria included an allergist or dermatologist diagnosis of active CIU. Exclusion criteria included use of systemic corticosteroids or other immunomodulatory agents (such as cyclosporine or sulfasalazine) in the month before enrollment due to their potential impact on basophil measures, and diagnosis of another skin disease (such as physical urticaria, atopic dermatitis, or urticarial vasculitis). After informed consent, patients completed a disease severity survey and underwent venipuncture under a Johns Hopkins Hospital institutional review board–approved protocol.

Disease survey

All subjects completed a disease survey containing 5 domains: demographic characteristics, presence of SCs, disease burden, elements of the urticaria severity score, and Skindex-29. Demographic characteristics included age, sex, race, and disease duration. Patients then indicated presence of SCs with concomitant hives in the lifetime of the disease. The SCs evaluated included gastrointestinal complaints, wheezing or breathlessness, palpitations, flushing, joint pain or swelling, and headache or fatigue. Patients who reported SCs with concomitant hives were categorized as CIU-SC, whereas those with no SCs were categorized as CIU-NSC.

The third domain assessed the disease burden. It included the number of systemic corticosteroid tapers, visits to the emergency department, days absent from work or school, and medication use.

The fourth domain contained elements of the urticaria severity score, a validated tool for monitoring urticaria severity.[9,10] The elements in the survey included number of wheals present at the time of survey, current itch score, and duration of individual wheals. The number and size of wheals was scored as follows: 0 for no hives; 1 for 1 to 10 small hives (<3 cm); 2 for 10 to 50 small hives or 1 to 10 large hives (≥3cm); 3 for more than 50 small hives or 10 to 50 large hives; and 4 for covered with hives. Itch was rated by a visual analog scale from 0 to 10, indicating no itch to severe itch. Wheal duration of individual wheals was scored as follows: 1 for less than 1 hour, 2 for 1 to 24 hours, and 3 for greater than 24 hours.

The fifth domain is Skindex-29, a 29-question dermatology survey assessing the impact of CIU on the quality of life (QOL) in the past 3 months.[10]

Basophil histamine release

Basophils from patient venous blood samples were isolated via Percoll density sedimentation to obtain mixed leukocytes with average basophil purity of 1% to 5%. Subsequent histamine release was stimulated by polyclonal goat antihuman IgE (0.01-3 μg/mL), and *N*-formyl-met-leu-phe (1 μmol/L) for 45 minutes at 37°C in calcium-containing buffers, as described.[7] Histamine release (HR) was quantified in cell-free supernatant with an automated fluorometric assay. Results were presented as the net percentages of total histamine content in total cell lysates of leukocyte aliquots after spontaneous HR percentages were subtracted from the total HR percentages. CIU histamine response was categorized as follows: HR of 10% or more as responders, HR of less than 10% as nonresponders. In some cases of significant basopenia, HR could not be defined. Total blood histamine content, an indirect measure of blood basophil numbers, was reported for 1 mL of blood.

Serum tryptase

Serum was stored at −20°C until assayed. Serum tryptase levels were measured using the UniCAP Tryptase Fluoro-Enzymatic Immunoassay, performed at Virginia Commonwealth University in Dr Lawrence B. Schwartz's Laboratory.

Statistical analysis

Comparisons between the CIU-SC and CIU-NSC groups were performed using unpaired *t* test. Correlation coefficients were found between serum tryptase level and (1) the number of SCs, (2) current wheal size/number score, and (3) current itch. A *P* value of less than .05 was considered statistically significant.

RESULTS

Patients' demographic characteristics and measure of disease

A total of 155 patients with a diagnosis of CIU completed surveys and venipuncture for analysis. Patients' characteristics are presented on the basis of presence or absence of SCs with concomitant hives, CIU-SC and CIU-NSC, respectively (Table I). Most patients in both groups were women, with average age in the 40s, and white. Notably, more than half of the CIU-SC group reported disease duration greater than 4 years, whereas less than a third of the CIU-NSC group reported the same outcome.

As compared with patients with CIU-NSC, patients with CIU-SC had significantly greater use of corticosteroid tapers in the past year, and in the lifetime of their CIU disease. There were also significantly higher frequencies of patients with CIU-SC than patients with CIU-NSC with emergency department visits in the past year and more than 1 day of work or school absences due to CIU.

SCs frequency and characteristics

Of the 155 study participants, 103 reported the presence of SCs with hive flares while 52 did not have SCs (Figure 1). The frequency of having 1 SC is 28%, 2 SCs is 19%, and 3 or more