Original Article

Recurrence of Chronic Urticaria: Incidence and Associated Factors

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What is already known about this topic? Recurrence is known to occur in a subset of patients with chronic urticaria.

What does this article add to our knowledge? This article delineates several characteristics of recurrent chronic urticaria, including a formal definition, frequency, and associated medication use.

How does this study impact current management guidelines? This study's findings that patients who require alternative therapies for chronic urticaria have a higher rate of recurrence may provide useful prognostic information for patients.

BACKGROUND: Chronic urticaria (CU) is urticaria that has been present continuously or intermittently for at least 6 weeks. Although the prevalence and characteristics of CU are well established, little is known about recurrent CU (RCU).
OBJECTIVES: We sought to establish a definition, determine the frequency, and evaluate risk factors for RCU.
METHODS: A retrospective chart review of adult patients with CU evaluated at the University of Texas Southwestern allergy and immunology clinic was performed. RCU was defined as CU recurring at least 6 months after cessation of controller therapy and resolution of prior CU symptoms. Charts were reviewed for symptom resolution and recurrence, subtypes of CU (idiopathic, physical, and urticarial vasculitis), and medication usage (first-line agents, alternative agents, and steroid dependence).
RESULTS: Forty-five of 341 patients (13%) had RCU. The recurrence group had a higher frequency of alternative agent use at 57.8% (n = 26) compared with the nonrecurrence group at 34.8% (n = 103), which was statistically significant ($P < .01$). The rate of steroid dependence was similar in both groups (13.3% in the recurrence group vs 14.5%) and not statistically significant. Individuals exposed to anti-inflammatory agents, immunosuppressants, and omalizumab had a significantly higher relative risk of recurrence compared with those who only used first-line agents (relative risk [RR] 2.32, $P < .01$; RR 2.69, $P < .01$; and RR 2.18, $P = .05$, respectively).
CONCLUSIONS: RCU occurs in approximately 13% of patients with CU in our clinic population. Alternative agent use and antihistamine refractoriness appear to place patients at increased risk for recurrence compared with first-line agent use alone. **© 2017 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Chronic urticaria; Chronic idiopathic urticaria; Physical urticaria; Urticarial vasculitis; Recurrent chronic urticaria*

Chronic urticaria (CU) is defined as urticaria that has been present continuously or intermittently for at least 6 weeks. In an overwhelming majority of cases, an external cause cannot be identified,[1-3] and these patients are labeled as having chronic idiopathic urticaria (CIU)[4] or chronic spontaneous urticaria.[5] Other subtypes of CU include physical urticaria and urticarial vasculitis.[6] In the United States, the prevalence of CU is estimated at approximately 1%. It predominantly affects adults, although children can also be affected, and has a female predominance.[7] For many patients, CU is an episodic and self-limited disorder, but the duration can vary considerably, with the average duration lasting 2 to 5 years.[8] Physical urticarias tend to have a longer duration than CIU and typically persist for several years.[9,10] In patients in whom no clear trigger has been identified, the spontaneous remission rate at 1 year has been estimated to be approximately 20% to 50%.[11-13] However, in up to 20% of patients, symptoms can persist for more than 5 years.[14] Duration and prognosis in this group has not been well studied.[11,13] Symptoms also recur in a subset of patients whose disease remains quiescent for some period of time while remaining off treatment.

CU can adversely affect a patient's quality of life[15] as it is physically uncomfortable, waxes and wanes unpredictably, interferes with daily life, and is often difficult to treat. Quality-of-life measures that are affected include negative mood changes, sleep deprivation, poorer social relationships, and general lack of energy.[16] There is much variability in the severity and duration of symptoms among individuals, and the underlying cause is not known in most cases, leading to patient frustration and anxiety.

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Abbreviations used
CIU- Chronic idiopathic urticaria
CU- Chronic urticaria
EMR- Electronic medical record
IRB- Institutional Review Board
RCU- Recurrent chronic urticaria
RR- Relative risk
UAS- Urticaria Activity Score
UTSW- University of Texas Southwestern

Although there have been multiple studies evaluating predictive factors for spontaneous remission,[10,13,17-19] there have been no studies investigating risk factors for the recurrence of CU to our knowledge. The objective of this study was to investigate the characteristics of recurrent CU (RCU) by establishing a definition, determining the frequency, and evaluating possible risk factors for recurrence.

METHODS

This was a retrospective chart review of patients who have been diagnosed with CU in the allergy and immunology outpatient clinic at the University of Texas Southwestern (UTSW) Medical Center in Dallas, Texas. Subjects were identified using an automated query of the electronic medical record (EMR) searching for the following keywords: "hives," "urticaria," or "chronic urticaria." Identified subjects were diagnosed with CU between January 2006 and January 2015.

Inclusion criteria

Any adult patients aged 17 years and older carrying a diagnosis of CU who had initial and follow-up notes available in the EMR were included.

Exclusion criteria

Subjects with the following characteristics were excluded (see Figure 1): age younger than 17 years, diagnosis of acute urticaria (defined as lasting less than 6 weeks in duration), alternative diagnoses, and inadequate clinical data.

Recurrence (RCU) was defined as CU that recurred at least 6 months after cessation of controller therapy and resolution of prior CU symptoms based on the experience of our clinical center. This information was determined based on information from the first to last clinical notes documented in the EMR. Charts were reviewed for resolution and recurrence of symptoms, subtypes of CU (eg, idiopathic, physical, and urticarial vasculitis), and medication usage (first-line agents, alternative agents, and steroid dependence). Patients were not contacted individually because of the limitations set forth by the Institutional Review Board (IRB) at UTSW related to the retrospective nature of this study. Patients with evidence of autoantibodies (eg, antithyroperoxidase antibodies) or those with autoreactive sera (eg, positive basophil activation assays such as the CU Index) were still considered to be idiopathic in line with the US Practice Parameters. First-line agents (agents in steps 1-3 of the US Practice Parameters) included all first- and second-generation H1 antagonists, H2 antagonists, and leukotriene receptor antagonists.[6] Alternative agents (step 4 care according to the US Practice Parameters) included anti-inflammatories (dapsone, hydroxychloroquine, colchicine, and sulfasalazine), immunosuppressants (cyclosporine, tacrolimus, and mycophenolate), and omalizumab. Steroid dependence was defined as daily dosing of systemic corticosteroids for the prevention of urticarial outbreaks for at least 1 month. Physical urticarias included phenotypes such as cholinergic, cold, delayed pressure urticarias, and dermatographism.

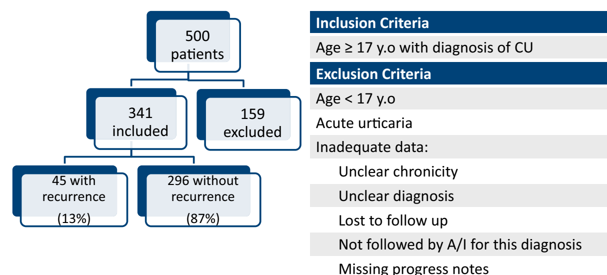

FIGURE 1. Patient breakdown and inclusion/exclusion criteria. This illustrates the initial sample size of 500 patients with 159 exclusions based on the criteria listed. The final sample size was 341 to include 45 patients with recurrence and 296 patients without recurrence. *A/I*, Allergy/Immunology; *CU*, chronic urticaria.

TABLE I. Patient characteristics

	Total (N = 341)
Age	
Mean (range, y)	44 (17% to 88%)
Gender, n (%)	
Male	91 (26.7%)
Female	250 (73.3%)
Ethnicity, n (%)	
African American	59 (17.3%)
Hispanic	20 (5.9%)
Caucasian	227 (66.6%)
Asian	20 (5.9%)
Unknown	15 (4.4%)
Alternative agent, n (%)	
Yes	129 (37.8%)
No	212 (62.2%)
Steroid dependence, n (%)	
Yes	49 (14.4%)
No	292 (85.6%)
Type of CU, n (%)	
Idiopathic	292 (85.6%)
Physical	44 (12.9%)
Urticarial vasculitis	5 (1.5%)

CU, Chronic urticaria.

Statistical analysis

Descriptive statistics were used for analysis. A χ^2 test was used to compare the recurrence groups with an alpha level of 0.05. Relative risks were calculated in reference to nonexposure to alternative agents. Statistical analysis used SPSS version 19 (IBM Corporation, Armonk, NY).

RESULTS

Of the 500 EMR charts reviewed, 159 subjects were excluded based on the criteria outlined in Figure 1. The characteristics of the subject cohort are outlined in Table I. Of the 341 subjects

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