



Original Article

Chronic Idiopathic Urticaria in Taiwan: A Clinical Study of Demographics, Aggravating Factors, Laboratory Findings, Serum Autoreactivity and Treatment Response

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Background/Purpose: Chronic idiopathic urticaria (CIU) is not uncommon, yet there is little information about the clinical features of CIU patients in Taiwan. The purpose of this study was to investigate the clinical features of CIU in Taiwan.

Methods: Patients with CIU were collected consecutively from the Urticaria Special Clinic in a medical center in northern Taiwan from December 2005 to May 2006. Clinical features and laboratory findings were studied. We also evaluated the therapeutic response of CIU patients with second-generation H1 receptor antagonist monotherapy for 6 weeks.

Results: A total of 62 CIU patients were investigated. The female to male ratio was 2.1:1 with a mean age of 31.8 years. The mean duration of the disease was 25.7 months (1.5–180 months). The most common aggravating factor was weather (79.7%), especially hot weather (50.8%). Fifty percent of the patients had atopy, and 37.3% of patients had positive autologous serum skin test. Besides, 61.3% of patients had at least one serum specific IgE antibody to the 18 common allergens examined. Finally, 60.7% of patients responded well to second-generation H1 receptor antagonist. Non-responders tended to have atopy ($p=0.0471$), especially allergic rhinitis ($p=0.0107$).

Conclusions: This study provided an overview of CIU patients in a medical center in northern Taiwan. We found that atopy did not influence the severity or duration of CIU. Nevertheless, atopy was associated with a poor therapeutic response of second-generation antihistamine. A survey of personal atopy history, especially allergic rhinitis, is important for management of CIU patients in Taiwan.

Key Words: atopy, autoimmune urticaria, autologous serum skin test, thyroid autoimmunity, urticaria

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Urticaria is a rather common disease worldwide, affecting 15–30% of the population.^{1–30} Thirty percent of the cases become chronic, which is defined as wheals with daily or almost daily appearance for more than 6 weeks.^{1,2} There are three main subtypes of chronic urticaria (CU), including physical urticaria (35%), chronic idiopathic urticaria (60%), and urticarial vasculitis (5%).³ Physical urticaria is traditionally included in the non-restrictive definition of chronic urticaria.² Based on the special eliciting physical factors, it is categorized separately in some classifications.⁴ Urticarial vasculitis presents as fixed wheals for more than 1 day with histologically proved vasculitis. What is not categorized above is chronic idiopathic urticaria (CIU). Up to 50% of patients with CIU were found to be related to an underlying autoimmune mechanism.⁵ Autologous serum skin test (ASST) is a clinical test that is generally available to detect autoreactivity in patients with CIU *in vivo*. Although many efforts and achievements had been done for CU in Taiwan,^{6–10} little information was mentioned about the clinical features of CIU in Taiwanese population. The aim of this study was to analyze the demographics, aggravating factors, laboratory findings, serum autoreactivity of patients with CIU in Taiwan. The effectiveness of therapy and prognostic factors are also discussed.

Methods

Patients

This study was conducted at the Urticaria Special Clinic of Department of Dermatology, National Taiwan University Hospital from December 2005 to May 2006 and had been approved by the Institutional Review Board/Ethics Committees of National Taiwan University Hospital. Written informed consents were obtained from patients. The patient population included subjects of 18 years old or older who had documented signs and symptoms of CIU for 6 weeks and had a CIU flare for 3 weeks or more, with urticarial lesions visible 3 days or more per week. Patients with a definite diagnosis of CIU were recruited consecutively in

this Special Clinic. Patients with physical urticaria or urticarial vasculitis, or receiving any antihistamines, corticosteroids, ketotifen, systemic antibiotics, nedocromil, sodium cromoglycate or thyroxin drug within 7 days preceding the study, were excluded.

Patients were subjected to a diagnostic protocol at the Day-7 (screening day, visit 1), including a complete history of possible causes and aggravating factors, past history and test of dermographism. All patients filled in a questionnaire, which was designed for the following data: demographic characteristics, personal and familial histories of atopic diathesis, duration of the disease and individual lesion, systemic diseases, and aggravating factors.

ASST

ASST was conducted at Day-7 by intradermal injection of 0.05 mL of fresh, sterile serum into the volar aspect of the forearm. An equal amount of sterile saline and histamine was injected into the other forearm as negative and positive controls. The result was evaluated after 30 minutes. Positive reaction was defined when the serum-induced wheal was red, with a diameter 1.5 mm wider than the saline-control.⁵

Laboratory investigation

Patients received laboratory investigation including complete blood cell counts with cell differentiation, erythrocyte sedimentary rate (ESR), aspartate aminotransferase (AST), alanine transferase (ALT), creatinine, anti-microsomal and anti-thyroglobulin antibodies, and Pharmacia CAP System fluoroimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden) for specific serum IgE antibodies to 18 common allergens at the screening day. A value of ≥ 0.35 kU/L (CAP-Class 1) was considered as positive.¹¹

Therapeutic protocol

Each patient received low-sedation, second-generation H1 receptor antagonist antihistamine monotherapy, either levocetirizine 5 mg or desloratadine 5 mg daily, for 6 weeks. Patients had visits on the Day-7 (screening day, visit 1), within 3 days

after Day 0 (baseline, visit 2), Day 14 ± 3 days (visit 3), Day 28 ± 3 days (visit 4), and Day 42 ± 3 days (visit 5). Evaluation of symptom scores for each patient was performed by an investigator at visits 2–5 (Table 1). Therapeutic response was assessed at visits 3–5 using the following scoring system: 1 = complete relief (virtually no signs/symptoms), 2 = marked relief (signs/symptoms greatly improved and cause little trouble), 3 = moderate relief (signs/symptoms present and troublesome but noticeably improved), 4 = slight relief (minimal improvement in signs/symptoms), 5 = treatment failure (signs/symptoms unchanged or worse than baseline). Patients were grouped according to the therapeutic response. Good responder was defined as complete or marked relief (score ≤ 2) at the visits 3–5. Non-responder was defined as slight relief or treatment failure (score ≥ 4) at the visits 3–5. The patients else were the poor-responders. The relationship of therapeutic response with demographics, ASST and outcomes of laboratory investigation was assessed. We also analyzed the influence of atopy or positive ASST on symptom scores.

Statistical analysis

Descriptive statistics was used to summarize the demographic and laboratory data. Continuous data was delineated by mean $\pm$ standard deviation. Categorical variables were described as *n* (%). Missing data was not included when calculating

percentage. Fisher's exact test and Wilcoxon Rank Sum Test were used to analyze categorical variables among the therapeutic response, ASST, and atopy. A *p* value of less than 0.05 was considered statistical significant. Logistic regression analysis was used to evaluate the relationship between atopy and ASST with symptom scores. Analyses were done with SAS software version 8.0 (SAS Institute, Cary, NC, USA).

Results

Demographic data

A total of 62 subjects with CIU were investigated. Of the 62 patients with CIU, 42 were female (68%) and 20 were male (32%) (female to male ratio = 2.1:1) (Table 2). Their age ranged from 18 years to 61 years (mean age, 31.8 ± 10.4 years; median, 29.5 years). The mean duration of the disease was 25.7 months (range, 1.5–180 months). The mean duration of individual lesion was 4.0 hours (range, from 10 minutes to 24 hours). Thirty-one patients (50%) had personal history of atopy and 28 (45.2%) patients had allergic rhinitis. Thirty patients (48.4%) had family history of atopy. Nine patients (14.5%) had family history of urticaria. The most common aggravating factor was weather (79.7%), especially hot weather (Table 3). Two of the 45 patients (4.4%) had angioedema. Twenty-two of the 59 patients (37.3%) had positive result of ASST. Six patients (9.7%) had thyroid disease.

Table 1. Symptom scores

Score	Pruritus	No. of hives	Size of largest hive (cm)	Interference with sleep	Interference with daily activities
0	None	None	None	None	None
1	Mild, minimal awareness, easily tolerated	1–6	< 1.25	Mild, not troublesome, adequate sleep	Mild, not troublesome, little effect on activity
2	Moderate, definite awareness, bothersome but tolerable	7–12	1.25–2.5	Moderate, awoke occasionally, average sleep	Moderate, some interference with activity
3	Severe, difficult to tolerate	> 12	> 2.5	Severe, substantial interference with sleep, poor sleep	Severe, daily activities substantially or completely curtailed

Table 2. Demographics of the 62 CIU patients in this study

Characteristic	n (%)
Sex	
Male	20 (32)
Female	42 (68)
Atopy	31 (50)
Allergic rhinitis	28 (45.2)
Allergic conjunctivitis	5 (8.1)
Atopic dermatitis	3 (4.8)
Asthma	5 (8.1)
Family history of atopy	30 (48.4)
Allergic rhinitis	22 (35.5)
Allergic conjunctivitis	3/62 (4.8)
Atopic dermatitis	2 (3.2)
Asthma	7 (11.3)
Family history of urticaria	9 (14.5)
Angioedema	2/45 (4.4)
Systemic disease	8/62 (12.9)
Thyroid disease	6/62 (9.7)
ASST	22/59 (37.3)

Laboratory tests

Five of 60 patients (8.3%) were noted to have autoimmune antibodies to thyroid [4 patients (7.3%) had anti-microsomal antibody, 2 (3.6%) had anti-thyroglobulin antibody]. Most of the patients had normal blood cell counts, AST and ALT. All the available data of serum creatinine was normal. Besides, 29.6% patients had increased sedimentation rate. Pharmacia CAP specific allergen tests revealed that *Dermatophagoides pteronyssinus* was the most common allergen (51.6%), followed by *Dermatophagoides farinae* (50%) and shrimps (25.8%) (Table 4). Thirty-eight patients (61.3%) had at least one serum specific IgE antibody to the 18 common allergens examined.

Therapeutic response

The response of low-sedation, second-generation H1 receptor antagonist antihistamine monotherapy for 6 weeks was evaluated. Thirty patients received desloratadine and 32 patients received levocetirizine. No significant difference of therapeutic efficacy was noted between the two treatment groups in 6 weeks ($p > 0.05$). Thirty-four

Table 3. Aggravating factors

Aggravating factors	n (%)
Food	32/58 (55.2)
Seafood	21/57 (36.8)
Egg	2/57 (3.5)
Peanut	9/58 (15.5)
Alcohol	12/57 (21.1)
Bamboo sprout	4/56 (7.1)
Taro	2/57 (3.5)
Fried chicken	2/57 (3.5)
Chili	13/57 (22.8)
Fruit	3/54 (5.6)
Emotion	23/58 (39.7)
Good	0/58 (0)
Bad	13/58 (22.4)
Stress	23/58 (39.7)
Season	31/59 (52.5)
Spring	9/57 (15.8)
Summer	21/59 (35.6)
Fall	9/58 (15.5)
Winter	16/56 (28.6)
Seasonal change	30/59 (50.8)
Weather	47/59 (79.7)
Hot	30/59 (50.8)
Cold	17/59 (28.8)
Exam	9/56 (16.1)
Before	8/56 (14.3)
After	2/49 (4.1)
Exercise	13/56 (23.2)
Skin condition	24/55 (43.6)
Dry skin	21/55 (38.2)
Oily skin	5/55 (9.1)
Bathing	26/54 (48.1)
Treatment	8/55 (14.5)
For common cold	5/54 (9.3)
Topical steroid	1/55 (1.8)
Topical cream	0/55 (0)
Topical Vaseline	0/55 (0)
Contact	31/55 (56.4)
Dust	19/55 (34.5)
Dog fur	3/55 (5.5)
Cat fur	3/5 (5.5)
Sweater	21/55 (38.2)
Detergent	6/55 (10.9)
Soap	2/55 (3.6)
Shampoo	2/55 (3.6)
Hair dye	2/55 (3.6)
Metal	10/55 (18.2)

Table 4. Results of CAP fluoroimmunoassay

CAP	n (%)
D1 (Dermatophagoides pteronyssinus)	32/62 (51.6)
D2 (Dermatophagoides farinae)	31/62 (50)
E1 (Cat dander)	6/62 (9.7)
E5 (Dog dander)	4/62 (6.5)
I6 (<i>Blatella germanica</i>)	12/62 (19.4)
M1 (<i>Penicillium notatum</i>)	0/62 (0)
M5 (<i>Candida albicans</i>)	5/62 (8.1)
F1 (Egg white)	0/62 (0)
F2 (Milk)	1/62 (1.6)
F3 (Fish; cod)	0/62 (0)
F13 (Peanut)	1/62 (1.6)
F14 (Soyabean)	1/62 (1.6)
F23 (Crab)	11/62 (17.7)
F24 (Shrimp)	16/62 (25.8)
F75 (Egg yolk)	0/62 (0)
F91 (Fruit)	1/62 (1.6)
M70 (<i>Pityrosporum orbiculare</i>)	1/62 (0)
M205 (<i>Trichophyton rubrum</i>)	5/62 (8.1)

patients (60.7%) were good responders, while five patients (8.9%) were non-responders. Seventeen patients (30.4%) belonged to the group of poor-responders. Non-responders were more likely to have allergic rhinitis ($p=0.0107$), personal history of atopy ($p=0.0471$), and specific IgE antibody to crab ($p=0.0321$).

ASST and symptom score

In addition, we evaluated if positivity of ASST had any influence about the baseline symptom score (visit 2). The result showed no statistically significance between positivity of ASST with pruritus, number of hives, size of the largest hive, interference with sleep, interference with daily activities, and sum of each patient's symptom score ($p>0.05$).

Atopy and symptom score

As for the relationship between atopy and baseline symptom score, atopy did not influence degree of pruritus, number of hives, size of largest hive, interference with sleep, and interference with daily activities and sum of each patient's symptom score ($p>0.05$).

Discussion

This is a prospective, analytic, cross-sectional, single-center study including 62 patients with CIU in Taiwan. The female preponderance in this study was in concordance with other European and Asian studies.^{2,12-14} Fifty percent of our patients were noted to have atopy. The most common associated condition was allergic rhinitis (45.2%), followed by asthma (8.1%), allergic conjunctivitis (8.1%) and atopic dermatitis (4.8%). For adults in Taiwan, the prevalence of atopy was 23.3%, allergic rhinitis was 17.9%, asthma was 3.5–7.8%, and atopic dermatitis was 5.0%.^{15,16} There was no data about the prevalence of allergic conjunctivitis in adults in Taiwan. Comparing with the information, our data implied that atopy, especially allergic rhinitis, occurred more frequently in patients with CIU than in the general adult population. Reviewing the literature,^{14,17} it is still equivocal if there is a link between CIU and atopy. Results were controversial and may be partially contributed to the definition of atopy. In Nassif's study, more than 90% of CIU patients examined had a personal history of atopic disease. Nassif¹⁴ defined atopy as the existence of one or more past or present recurrent items previously diagnosed by a physician: asthma and/or eczema and/or allergic rhino-conjunctivitis. When defining atopy more strictly with personal history of atopic diseases and sensitization to at least one common allergen confirming by positive skin prick tests in Aughey et al's study,¹⁷ the results did not support the hypothesis that chronic urticaria affects mostly atopic patients. However, they still found that 43% of the studied chronic urticaria patients had personal history of atopy.¹⁷ In addition, our study revealed that atopy did not influence disease severity or disease duration of CIU; nevertheless, it was associated with poor therapeutic response of second-generation antihistamine with standard dose in our patients with CIU. We proposed a survey of personal atopy history especially allergic rhinitis is important for managing patients with CIU in Taiwan, because it may predict poor responders for standard dose of antihistamine

treatment. On the other hand, the current guidelines have advocated that increased dosing of second-generation antihistamines up to four-fold benefit patients with urticaria who do not respond to standard doses.¹⁸ Second-generation antihistamines with higher doses might have additional anti-inflammatory or immunomodulatory effects to control refractory urticaria.^{18,19} For patients with atopy, treatment with higher dosage of second-generation antihistamines may be needed to control disease activity of CIU. Therefore, it should be further studied if atopy is still associated with poor therapeutic response of second-generation antihistamine with higher dosage.

There is emergence of evidence that up to 50% of patients with CIU could be explained by an underlying autoimmune basis involving anti-high affinity IgE receptor (FcεRI) antibodies or anti-IgE antibodies.⁵ These antibodies are functional, leading to mast cell and basophil activation and release of histamine and other pro-inflammatory mediators.³ Although the basophil histamine release assay (HRA) remains the gold standard investigation to detect functional autoantibodies *in vitro*, it is time consuming with high inter-assay variability and can be carried out only in selected centers.²⁰ ASST therefore is a more popular screening *in vivo* test to detect basophil histamine-releasing activity when HRA is not available. A correlation between the presence of anti-FcεRI and anti-IgE autoantibodies and positive ASST was documented.²¹ It has a sensitivity of 70% and specificity of 80%.³ It elicits an immediate wheal-and-flare response in 30–50% of CIU patients.^{3,12,20} In our study population, 37.3% of them showed a positive reaction to ASST, which was close to the previous reports.^{3,8} In addition, some studies showed that patients with positive ASST presented more severe clinical features than serum-negative subjects.^{12,22} Such a phenomenon was further studied that basophils of patients with CIU had altered IgE receptor-mediated degranulation. *Ex vivo* activation of the blood basophils with an optimal dose of cross-linking anti-IgE antibodies was grouped into two phenotypes based

on the degree of histamine release: responder ($\geq 10\%$ histamine release) and nonresponder ($< 10\%$ histamine release). Basophils of CIU patients with a responder phenotype had reduced Src-homology 2-containing—5'-inositol phosphatase (SHIP)-1 protein levels, an inhibitor in the FcεRI histamine degranulation pathway.²³ This may explain partially that CIU patients with positive ASST reported more disease severity. However, in our study, we found that the severity of attacks was not higher in subjects with positive ASST. This may be due to the followings: (1) our sample size was too small to elucidate the clinical significance of ASST with CIU; (2) auto-reactivity accounted only partially for the etiology of CIU (still 41% of patients with CIU had no identified factor,⁵ other cellular or subcellular, rather than humoral factors may be involved in the pathogenesis and influence disease severity);²⁴ (3) these autoantibodies were also detected in subjects in remission and even in normal subjects, and the antibody functional activity may also depend on the receptor being occupied by its natural ligand;¹¹ and (4) ASST does not actually prove the presence of antibodies, but rather shows histamine-releasing properties of the tested serum.²⁵ Therefore, ASST cannot be used alone to predict the severity of urticaria and may not be sufficient to define CIU as "autoimmune".²⁵

The association of CIU with thyroid autoimmunity has been studied.²⁵ Thyroid autoimmunity was more prevalent in CIU patients (14–29%) than in population controls (5–6%).^{7,26} It has been postulated that thyroid autoimmunity may play a role in the pathogenesis of CIU, but most studies have suggested that antithyroid antibodies (ATA) are not a direct causative agent in CIU.^{27,28} It appears more likely that ATA and anti-IgE receptor antibodies are associated, parallel, auto-immune events.²⁸ In the present study, only 7.3% patients had antimicrosomal antibodies and 3.6% had antithyroglobulin antibodies, which were lower than in previous studies.^{13,29,30} Our data suggested that the association of thyroid autoimmunity is not so prevalent in Taiwanese CIU patients. The result may be influenced by the less specific thyroid

microsomal antibodies and small sample size for the low prevalence of thyroid auto-immunity.

Due to the high proportion of atopy noted in the study, we evaluated 18 common allergen specific IgE antibodies by Pharmacia CAP System specific allergen test. Results showed that 61.3% of patients had at least one serum specific IgE antibody to the 18 common allergens. This may contribute to high proportion of atopy in our study. Thirty-two patients (51.6%) were noted to have specific IgE to *Dermatophagoides pteronyssinus*. In these 32 patients, 19 patients had atopy (including 1 atopic dermatitis, 5 asthma, 17 allergic rhinitis, and 2 allergic conjunctivitis). We further analyzed if there was any difference between positive *Dermatophagoides pteronyssinus* group (32 patients) and negative *Dermatophagoides pteronyssinus* group (30 patients) about disease duration, symptom scores and therapeutic response. Yet, all the data revealed no statistical significance ($p > 0.05$).

In conclusion, this study provided a clinical analysis of patients with CIU in Taiwan. We found female predominance and increased prevalence of atopy. Besides, atopy did not influence disease severity or duration of CIU but the therapeutic response of second-generation antihistamines. About 60% of the patients had good response to low-sedation, second-generation H1 receptor antagonists. Non-responders were more likely to have atopy, especially allergic rhinitis. Additional multicenter studies with a larger sample size and longer duration of treatment are warranted to characterize patients with CIU in Taiwan.

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