

Chronic urticaria in Chinese population: a hospital-based multicenter epidemiological study

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Abstract

Background: The epidemiologic profiles of chronic urticaria (CU) vary considerably among regions, and few such data are available from China.

Methods: We performed a multicenter open questionnaire investigation about the clinical and laboratory features of CU, defined as recurrent wheals with/without angioedema lasting for ≥ 6 weeks, among 3027 patients.

Results: Female preponderance was observed (female/male ratio, 1.46 : 1). The mean age at diagnosis was 34.7 ± 13.8 years, and the mean disease duration was 18.5 ± 46.1 months (range, 1.5–127 months). Patients were classified as having chronic spontaneous urticaria (CSU, 61.0% of patients), physical urticaria (PU, 26.2%), or other urticaria types (OU, 2.3%). Nocturnal attacks were reported by 60% of cases. The Urticaria Activity Score (UAS) in patients with CSU was 3.8 ± 1.4 . The mean Dermatology Life Quality Index was 7.3 ± 3.4 (range 0–30). Induction or exacerbation of wheals with alcohol drinking was reported by 55.7% of patients. Chronic hepatitis B was less prevalent in our CU patients compared with the general Chinese population (2.7% vs 7%). Positive autologous serum skin tests (ASSTs) were observed in 66.9% of patients. Patients with positive ASST had higher UAS, greater angioedema frequencies, longer disease durations, and poorer QoL compared with patients with negative ASST ($P < 0.05$).

Conclusion: In this Chinese population, CU usually affected youth, and CSU was the most common subtype. Autoreactivity and alcohol consumption were the top two triggers for CU, whereas latent infectious and chronic inflammatory diseases were not as common as in previous reports.

Chronic urticaria (CU) is a distressing and common skin disorder characterized by recurrent wheals and/or angioedema lasting for ≥ 6 weeks (1). The pathogenesis of CU is unclear, although possible causes may include chronic infections, allergy to food or food additives, stress, and autoantibody production against immunoglobulin E (IgE) receptor. Age, race, sex, occupation, geographic location, and seasonal variations may be differentially implicated in the clinical features of CU. However, a lack of knowledge of their significance may lead to different guidelines for clinical classification and therapeutic interventions in different countries. Given the limited epidemiologic data about CU that are available in Asia (especially from China), we performed a hospital-based multicenter cross-sectional epidemiologic survey of CU in Chinese population.

Methods

Patients

This prospective, cross-sectional, hospital-based epidemiologic investigation was performed from January to September in 2011. This study involved patients diagnosed with CU in 19 tertiary referral hospitals, which were widely distributed in different provinces of China. Diagnosis of CU was made by specialists (i.e., members of the Urticaria Investigation Group of the Chinese Dermatology Association) according to the criteria published in the EAACI/GA2LEN/EDF/WAO guideline (1). This guideline was also used to categorize urticaria cases into the following three types: chronic spontaneous urticaria (CSU), physical urticaria (PU; including delayed physical urticaria, cold/heat contact urticaria, solar urticaria, and dermatograph urticaria), and other types of urticaria (OU; including aquagenic, cholinergic, contact, and exercise-induced urticaria).

The Urticaria Activity Score (UAS) was used to evaluate the disease activity once daily for 7 days according to the EAACI/GA2LEN/EDF guideline (1). At the first visit, UAS was evaluated by the physician and the patient. On the subsequent 6 days, UAS was self-evaluated by the patient on a diary card. The average score was calculated after 1 week.

All enrolled patients completed a specific survey containing 40 questions regarding their general demographic characteristics, disease duration, frequency and duration of each episode, age of onset, triggering factors (e.g., alcohol consumption), previous and present treatments, etc. The Dermatology Life Quality Index (DLQI), a validated questionnaire on the quality of life (QoL) of dermatology patients, was analyzed for some patients during the survey. Cronbach's alpha (0.79) indicated internal consistency of the questionnaire. The total DLQI score was calculated by summing the score of each of the 10 questions and was interpreted as no (0–1), mild (2–5), moderate (6–10), severe (11–20), or very severe impairment (21–30) of QoL (2).

Ten of the 19 hospitals performed the autologous serum skin test (ASST) according to the previously described methods and criteria (3). All operators were trained in a standardized manner before the start of the study. The study was

approved by the Ethics Committee of Southwest Hospital. Written informed consent was obtained from all patients prior to their participation in the investigation.

Statistical analysis

For continuous variables, the mean $\pm$ standard deviation (SD) was reported, according to the data distribution. Statistically significant differences between the means were determined by the *t*-test or Mann–Whitney *U*-test, with $P < 0.05$ indicating statistical significance. The reliability and internal consistency were assessed by Cronbach's alpha coefficient, with $\alpha \geq 0.70$ being considered satisfactory. Statistical analysis was performed with the Statistical Package for the Social Sciences (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics

The demographic characteristics of the 3027 patients who were diagnosed with CU and enrolled in this study are summarized in Table 1. Most patients (49.8%) were 20–39 years of age. Although most patients were female, female predominance was not seen in patients <20 years of age (female/male, 225: 271). According to the standard classification of occupations of P.R. China, the three most common occupations were commerce and service personnel, functionary and management, and professional and technical personnel. Most patients (36.0%) had a junior college or above education level.

Table 1 Demographic characteristics of chronic urticaria in Chinese population

Parameter	N (%)
Sex	
Female	1795 (59.3)
Male	1232 (40.7)
Age (years)	34.7 $\pm$ 13.8
Education	
Junior college or above	1089 (36.0)
Vocational/high school	755 (24.9)
Junior middle school	797 (26.3)
Elementary school	386 (12.8)
Occupation	
Commerce or service personnel	560 (18.5)
Workers	162 (5.4)
Farmers and fishers	209 (6.9)
Professional and technical personnel	283 (9.3)
Managers	314 (10.4)
Clerical people	207 (6.8)
Police and soldiers	25 (0.8)
Other	1267 (41.9)

Data are presented as *n* (%) except for age, which is presented as the mean $\pm$ SD.

Clinical characteristics

The classification of 2710 cases of CU (271 cases were excluded due to a lack of documented classification), according to the EAACI/GA2LEN/EDF/WAO guideline, is summarized in Table 2. The most common type was CSU, followed by PU and OU. The mean age of the first CU attack was 31.0 ± 14.1 years. Most patients experienced their first attack at 20–39 years (50%), followed by 40–59 years (24%), <20 years (23%), and ≥ 60 years of age (3%). Patients with OU had an earlier onset age (23.1 ± 10.4 years) than the total age of onset (31.0 ± 14.1 years) ($\chi^2 = 13.38$; $P < 0.05$).

The mean duration of the disease course was 18.5 ± 46.1 months. Most patients reported a disease duration of ≤ 6 months (72.6%), followed by 7–24 months (18.4%), > 60 months (13.1%), and 25–60 months (8.4%). There was no significant difference in CU duration between the three types of urticaria ($P > 0.05$).

In terms of the duration of individual episodes, 86.2% of patients with CU reported that wheals usually lasted < 24 h. The mean duration of individual episodes was shorter for PU than for CSU. For example, 94.8% (732 of 772) of PU cases reported that individual attacks lasted < 4 h, compared with 30.7% (567 of 1834) of CSU cases. The mean UAS was 3.8 ± 1.4 (no significant difference by gender). Nocturnal urticarial attacks were reported by 60% of patients. More patients with CSU had concurrent angioedema (28.8%) compared with patients with PU or OU ($\chi^2 = 78.71$, $P < 0.001$).

Impact on QoL

Sleeping and emotional disorders

Among 2602 CU patients, 1137 cases (52.2%) reported sleeping disorders (with data lacking in 425 cases). The percentage of sleep disorders was higher among patients with CSU compared with patients with PU or OU ($\chi^2 = 13.95$, $P = 0.039$). Among the 2860 patients for whom data were available, 14% (276 cases) reported emotional disorders, including anxiety

(247 patients, 9.2%) and depression (129 patients, 4.8%). A greater percentage of patients with OU reported having anxiety compared with patients with CSU or PU ($\chi^2 = 13.38$, $P = 0.037$).

Results of the DLQI questionnaire

The DLQI questionnaire was completed by 858 CU patients. This subgroup of patients had a mean age of 34.5 ± 13.5 years, a female/male ratio of 1.4 : 1, and mean disease duration of 18.6 ± 43.3 months. The distribution by urticaria type was 68.4% CSU, 30.0% PU, and 1.6% OU. There was no difference in the duration of CU between the three urticaria types. The DLQI scores of the 858 patients with CU are summarized in Table 3.

The total DLQI score was 7.3 ± 3.4 (range, 0–30), indicating 'moderate impairment of QoL'. No significant differences were observed between males and females in the total DLQI score or for each question score. Compared with patients with primary education or beyond, patients with higher education (junior college or above) reported significantly higher impact on QoL for question 2 (embarrassment) ($P < 0.05$). The DLQI score of patients with CSU was higher than that of the other two types ($P < 0.01$). Longer disease duration was associated with significantly lower scores for questions 1 (symptoms) and 4 (clothing), but higher scores for questions 2 and 7 (work/study).

The DLQI score was positively correlated with the duration of individual wheals ($r = 0.82$). Among 858 patients undergoing DLQI investigation, the incidence of angioedema was higher in patients with CSU (29.03%) compared with the other two types ($\chi^2 = 78.71$, $P < 0.001$). Concurrent angioedema was associated with worse DLQI scores, even after adjustment for gender, age, disease duration, and education ($P < 0.01$).

Possible causes

Daily alcohol consumption was reported by 687 (25.4%) patients, among whom 383 (55.7%) patients reported an

Table 2 Detailed distribution of different types and subtypes of chronic urticaria

Type	Male (n/%)	Female (n/%)	Total (n/%)
Chronic spontaneous urticaria	732 (39.7)	1113 (60.3)	1845 (68.1)
Physical urticaria	330 (41.6)	464 (58.4)	794 (29.3)
Delayed pressure urticaria	4 (28.6)	10 (71.4)	14 (0.5)
Cold contact urticaria	31 (34.1)	60 (65.9)	91 (3.0)
Heat contact urticaria	25 (49.0)	26 (51.0)	51 (1.7)
Solar urticaria	3 (50.0)	3 (50.0)	6 (0.2)
Dermographic urticaria	267 (42.2)	365 (57.8)	632 (20.9)
Other types of urticaria	58 (81.7)	13 (18.3)	71 (2.6)
Aquagenic urticaria	1 (50.0)	1 (50.0)	2 (0.1)
Cholinergic urticaria	54 (84.4)	10 (15.6)	64 (2.1)
Contact urticaria	3 (75.0)	1 (25.0)	4 (0.1)
Exercise-induced urticaria	0 (0.0)	1 (100.0)	1 (0.0)

Table 3 Dermatology Life Quality Index (DLQI) score of patients with chronic urticaria (CU)

Attribute	DLQI score	P-value
Total	7.49 ± 3.69	
Sex		
Male	7.47 ± 3.70	0.061
Female	7.50 ± 3.72	
Clinical subtypes		
Chronic spontaneous urticaria	7.60 ± 3.79	0.007
Physical urticaria	7.13 ± 3.54	
Other types of urticaria	6.55 ± 3.02	
Angioedema		
With	8.13 ± 3.75	0.006
Without	7.34 ± 3.69	
ASST		
Positive	7.88 ± 3.62	0.011
Negative	7.38 ± 3.56	

induction or exacerbation of wheals associated with alcohol drinking. In the 514 patients who smoked, only 16 cases (3.1%) reported smoking-induced wheals. In >70.0% of CU cases, there was no association of attacks with seasonal variations. Among 671 patients with CSU, temperature change (484 patients, 72.1%), physical pressure (66 patients, 9.8%), and emotional stress (33 patients, 4.9%) were the three most common triggering factors of CU. Self-reported rates of drug allergy and food allergy in CSU patients were 4.0% and 21.6%, respectively. An association between wheals and menstruation was observed in 53 (4.8%) of the 1113 female patients with CSU.

Concomitant diseases were found in 542 of 1845 patients (29.4%) with CSU. These diseases included digestive disorders (143 patients, 26.4%), endocrine disorders (43 patients, 7.9%), and hypertension (34 patients, 6.3%). In terms of concomitant inflammatory or infectious diseases, chronic gastritis (95 patients, 7.3%), chronic hepatitis B (35 patients, 2.7%), tonsillitis or otitis media (21 patients, 1.6%), and urethritis or vaginitis (9 patients, 0.7%) were reported among 1303 patients.

An autologous serum skin test (ASST) was performed in 390 patients with CSU, of which 261 cases (66.9%) showed positive reactions. Nine of the 19 hospitals did not perform this test. To verify that the tested group was representative of the whole cohort of patients, we conducted a supplementary analysis. We compared the demographic characteristics of the 390 patients who underwent ASST to those of the 1845 CSU patients. We found no significant difference in demographic and clinical characteristics between the two groups (data not shown). Among the patients with positive ASST, females were more common ($P < 0.05$). UAS of patients with positive ASST was higher than that of patients with negative ASST (4.0 ± 1.3 vs 3.7 ± 1.6 , $P < 0.05$). Patients with a positive ASST had poorer QoL (DLQI, 7.88 ± 3.62 vs 7.38 ± 3.56 , $P < 0.05$), longer wheal duration ($P < 0.05$), and higher prevalence of angioedema ($P < 0.001$), compared with patients with negative ASST, as shown in Table 4.

Discussion

This study represents the first nationwide epidemiological survey of CU in China. We observed a female predilection for CU, consistent with prior studies (4). The mean age of patients and the mean age of onset were similar to those in a previous report (5).

In our series, 36.0% of the patients had completed junior colleges or higher level of education, which is above the average proportion at 21.5% in China, according to the 6th national population census conducted in 2011 (<http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.html>). Such difference may be caused by the following factors: (i) the present study is a hospital-based survey, and all of the 19 participating centers are tertiary referral hospitals located in provincial capital or central city; (ii) most patients visiting these hospitals have better financial condition and medical insurance; and (iii) the sample size in the present study is relatively small considering

Table 4 Clinical characteristics among autologous serum skin test (ASST)-positive and ASST-negative patients

Characteristic	ASST-positive	ASST-negative	Total	P-value
Sex				
Female	190 (72.8)	78 (60.5)	268	0.004
Male	71 (27.2)	51 (39.5)	122	
Itching				
None	0	0	0	0.435
Mild	13 (5.0)	20 (15.5)	33	
Moderate	146 (55.9)	64 (49.6)	210	
Severe	102 (39.1)	45 (34.9)	147	
Wheal duration				
Several hours	208 (79.7)	118 (91.5)	326	0.031
1 day	26 (10.0)	5 (3.9)	31	
>1 day	27 (10.3)	6 (4.7)	33	
No. of wheals				
None	0	0	0	0.890
<20	40 (15.3)	20 (15.5)	60	
20–50	120 (46.0)	54 (41.9)	174	
>50	101 (38.7)	55 (42.6)	156	
Angioedema				
With	91 (34.9)	16 (12.4)	107	<0.001
Without	170 (65.1)	113 (87.6)	283	

a total of 1.3 billion Chinese population. All these factors may lead to inevitable selective bias to some extent.

The etiology of CU is very diverse, and the identified triggers vary in different studies. Chronic infection and inflammation have been described as important contributing factors to CU in 2010 AADV consensus guidelines (6). The EAACI/GA2LEN/EDF/WAO guidelines recommend that patients should be examined and treated for gastrointestinal tract infection caused by *Helicobacter pylori* or bacterial infections of the nasopharynx (7). Chronic inflammatory processes, particularly gastritis, reflux esophagitis, and inflammation of the bile duct or gall bladder, have been implicated in the induction of CSU, but prevalence data are lacking (7). In our results, the prevalence rates of chronic gastritis, chronic hepatitis, tonsillitis or otitis media, and urethritis or vaginitis were all lower than those in the general population in China. For example, only 2.7% of our CU patients had chronic hepatitis B, which is far below the 7% national prevalence of this disease in China. Case-control studies and cohort research are needed to explore the link of chronic gastritis and chronic hepatitis B with CU.

Among our CSU patients, 74 (4.0%) reported drug allergies, including 28 antibiotics, 24 compound antipyretic analgesic, 16 traditional Chinese medicine (TCM), and others. This low prevalence of association with drug in our series is significantly different from the published data in the literature (8). CU is actually considered as a nonallergic skin disease induced by activation of mast cells (9). Some drugs such as NSAIDs, codeine, and morphinic agents can induce or aggravate CU by a direct action on mast cell degranulation (9). In our results, all of 24 compound antipyretic analgesics contained NSAIDs. Although we did not perform challenge test, the constellation of chronic urticaria and asthma

induced by NSAID is clinically rarely observed in Chinese patients. In recent years, some single nucleotide polymorphisms (SNPs) related to the prostaglandin and leukotriene pathways have been found to link to NSAID-induced asthma, urticaria, and angioedema, including LTC4S, ALOX5, ALOX5AP, and in CysLT and PTG receptors (10). It remains to be determined whether there are differences in genetic susceptibility between Chinese and Western population.

The self-reported food allergy rate was 21.6% among our CSU patients, consistent with another Chinese study (11), but higher than data from Western countries (12). Nevertheless, the actual rate of food-induced CU, as demonstrated by open food challenge and double-blind, placebo-controlled food challenge test (DBPCFCT), is rare. Moreover, the CU symptoms did not improve after the suspected culprit food was removed from the daily diet (4). Therefore, we suspect that the actual food allergy rate, in the absence of a positive DBPCFCT, is much lower than the self-reported food allergy rate and that daily food allergens have less of an effect in the pathogenesis of CU.

Positive ASST was found in two-thirds of CU cases. In the case of a positive ASST, also known as autoreactive chronic urticaria (ACU), the IgG antibodies play an important role by interacting with the α chain of the high-affinity IgE receptor (Fc ϵ RI α). Although the prevalence and significance of ASST in CU have been widely investigated, the positive rate of ASST varies widely between different studies. We found that 66.9% of CSU patients (261 of 390) had a positive ASST, with female predominance. Moreover, patients with a positive ASST had higher disease activity scores, higher frequencies of angioedema, and poor QoL. This is consistent with previous research (13, 14) and our previous data from single center (3). This information may be helpful for determining a subtype-specific therapeutic schedule.

Alcohol consumption was associated with the induction/exacerbation of urticarial wheals in 55.7% of patients who consumed alcohol daily. To date, no existing study has addressed whether alcohol consumption could be a triggering factor for CU. A true IgE-mediated allergy to alcohol or its metabolites (acetic acid and acetaldehyde) has rarely

been described in the literature. Further studies and allergy tests are required to determine whether this effect is caused by an IgE-mediated immediate hypersensitivity reaction or a nonspecific elicitation of the release of histamine and other mediators. Reactions to additives, such as sulfites, in certain alcoholic beverages should also be ruled out in such patients.

Limitations

This study has some limitations. This is a hospital-based survey that cannot avoid some selective bias. Our data were based on patient report and recall on questionnaires. We did not determine the concurrent presence of active *H. pylori* infection in patients with CSU and chronic gastritis. Some routine laboratory tests, including whole-blood count and autoantibody detection, were not performed. Furthermore, we did not determine the final course of disease by long-term follow-up. Finally, because participants were recruited from multiple centers, it was not possible to avoid selective bias due to a nonhomogeneous population and spatial distribution.

Conclusion

In conclusion, this study provides a profile of CU in a Chinese population. CSU was the most common subtype in our population. Autoreactivity and alcohol consumption were the top two triggers of CU, whereas latent infectious and chronic inflammatory diseases were not as common as in previous reports.

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Conflicts of interest

None.

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