

Refractory Chronic Urticaria in Adults: Clinical Characterization and Predictors of Severity

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Abstract

Background: Chronic urticaria (CU) is defined as recurrent urticaria lasting for more than 6 weeks.

Objectives: We aimed to characterize the phenotypes of patients with CU refractory to standard dose anti-H1 antihistamine treatment and search for clinical predictors of poor disease control.

Methods: Retrospective collection of data regarding clinical characteristics, manifestations, comorbidities, treatment, and disease control of all adult CU patients presenting to the Allergy and Immunology Department during one year. Descriptive and inferential analysis was performed to search for factors associated with disease control.

Results: Sixty-one adult patients were included, 74% females, average age 44.5 years (18 to 84 years old). Most patients (78.7%) had initiated CU less than 1 year before enrolment. Chronic spontaneous urticaria (CSU) accounted for 55.7% of the patients and chronic inducible urticaria (CIndU) for 44.3%. Angioedema was present in 55.7% of the patients. Evidence for autoimmunity (positive anti-thyroid peroxidase antibodies, anti-nuclear antibodies or autologous serum test) was found in 38.8% (n=19) of 49 tested patients. High C-reactive protein was present in 20.7% of 29 patients evaluated; half of these also had positive antinuclear antibodies. Forty-six patients (75.4%) had at least one significant exacerbation, requiring medical appointment, emergency room, hospitalization or job absenteeism. The number of exacerbations correlated with the presence of angioedema ($p=0.022$), with a recent diagnosis (<1 year), and with higher UAS7 severity ($p=0.006$). CIndU associated with poor symptom control ($p=0.022$) but had less exacerbations requiring medical observation or hospitalization ($p=0.015$).

Conclusions: About one third of patients with CU presented autoimmunity. UAS7 severity and Angioedema are associated with disease exacerbations. UAS7 and UCT presented unequal accuracy, with UAS7 better associating with the occurrence of exacerbations and treatment doses. Accurate diagnostic tests, namely autoimmune parameters and inflammatory markers, should be recommended in some individual cases.

Background

Urticaria is a mast-cell-driven disease characterized by the development of transient pruritic wheals with or without associated angioedema(1). This definition excludes other medical conditions in which wheals, angioedema or both may occur, such as anaphylaxis, auto-inflammatory syndromes, vasculitic urticaria or bradykinin-mediated angioedema, including hereditary angioedema(2).

Chronic urticaria (CU) is defined by the presence of recurrent urticaria, angioedema, or both, for a period of six weeks or longer(2, 3). In most patients, CU is a self-limited disorder, with an average duration of two to five years. However, in up to 30% of the patients, the symptoms may persist for more than five years(4, 5).

Chronic urticaria is a common disorder, with a lifetime prevalence of approximately 10–20% in the general population(2). The estimated prevalence of CU is up to 1% in the United States, 7.8% in Germany, 9.0% in Southwest Norway and 3.4% in Portugal(4, 6–8). CU is more common in adults than in children, and women are affected twice as often as men^{9,10}. The condition typically begins between the third and the fifth decades of life(6, 9).

The EAACI/GA²LEN/EDF/WAO consensus(2, 3) classified CU into two subtypes for clinical use: (1) chronic spontaneous urticaria (CSU), when no specific eliciting factors are identified, or (2) chronic inducible urticaria (CIndU), when specific stimuli trigger the symptoms. CIndU include symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria and aquagenic urticaria. Two or more different subtypes of urticaria may coexist in any given patient.

The diagnosis of CU is based on clinical history, physical examination and the exclusion of some specific causes or aggravating factors, such as newly administered drugs (e.g. nonsteroidal anti-inflammatory drugs – NSAIDs and hormonal therapies), infections (viral, bacterial and parasitic), IgE-mediated allergic reactions, insect stings, emotional stress, alcohol and some dietary habits (e.g., spicy food)(2, 10, 19, 20, 11–18).

Complementary laboratory tests (erythrocyte sedimentation rate, C-reactive protein, blood count, complement factors, antinuclear antibodies, cryoglobulins, hepatitis B and C serologies, serum protein electrophoresis, thyroid function and others) are recommended only in cases in which the clinical history suggests an underlying etiology(2, 20, 21). Autoimmunity, due to IgG and/or IgE autoantibodies, has been proposed as an etiology of CSU(22). It may be investigated upon clinical suspicion by the autologous serum skin test or other markers such as antinuclear antibodies (ANA) or antithyroid antibodies(23). Skin biopsy may be performed in cases of suspected vasculitic urticaria, particularly in CU refractory to antihistaminic treatment, with individual painful lesions rather than pruritic, with purpuric lesions, or when systemic symptoms are present, such as arthralgias and/or fever(24).

The prospective study AWARE (Germany) analyzed 1550 patients with H1 anti-histamine-refractory CSU in a 1-year non-interventional trial. In this study, 59.1% of the patients had papules at least once in the last 6 months, 16.1% reported at least 1 episode of angioedema, and 28.2% had moderate/high/very high impact on quality of life, namely due to pruritus, sleep disturbance and mental status disorders(25). Regarding control medications, 17.4% of the patients were not following guideline recommended CU treatment(25).

A similar AWARE study was conducted in Portugal and included 76 patients(26). It showed that both wheals and angioedema independently affect chronic urticaria quality of life questionnaire (CU-QoL)(26). Guideline recommended non-sedative H1-AH treatment was used in almost 91.0% of patients at enrollment(26). A total of 43.9% had moderate to severe urticaria, out of which 35.4% were medicated

with third line therapy (omalizumab or cyclosporine), while 10.8% used oral corticosteroids, a lower percentage compared to the study performed in Germany(25).

The objectives of our study were: (1) to characterize the clinical features, subtypes, cofactors, treatment and disease control status in adult CU patients followed in an Allergy and Immunology Department (2) and to look for clinical and laboratorial predictors of poor disease control (including both exacerbations and symptom control).

Methods

This is a retrospective, cross-sectional, and inferential study that included all adult patients with medically-confirmed diagnosis of CU (as defined by EAACI guideline(2)), refractory to approved doses of H1-antihistamines, that were observed at the outpatient clinic of the Allergy and Immunology Department of Centro Hospitalar e Universitário de Coimbra, Portugal, during one year.

Disease characteristics outcomes

Patients were evaluated and characterized according to demographic data, subtypes of urticaria, angioedema, medically diagnosed psychiatric disorders, asthma and atopic diseases, as defined by the European Academy of Allergy and Clinical Immunology and Global Initiative for Asthma. Arterial hypertension was defined by the European Society of Cardiology(27) and type 2 diabetes by the European Association for the Study of Diabetes and American Diabetes Association(28). Obesity was defined as a body mass index greater than 30 kg/m². Diagnostic work-up and treatment data were collected from the medical records at the same time as CU control was evaluated, using two methods:

1. Significant exacerbations – defined as CU exacerbations that required unscheduled medical consultations, emergency room admission, hospitalization or job absenteeism during the previous year;
2. Activity and disease control scores: Urticaria Control Test (UCT)(29) and Urticaria Activity Score 7 (UAS7)(30).

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 24.0®. Descriptive statistics were analysed as mean and standard deviation for the variables with normal distribution, and median and interquartile range for the variables without normal distribution. Variables were also described in absolute number (n). The nominal variables were compared using Pearson's chi-square test or Fisher's exact test according to Cochran's rules. The normal distribution of the ordinal variables was evaluated using the Kolmogorov-Smirnov test (considering a population sample of more than 30 individuals in both groups). The comparison of these variables was tested using Student's T-tests (parametric test, applied after verifying the homogeneity of variances by the Levene test) or Mann-Whitney test (non-parametric test). A Type I error of 0.05 was considered.

Results

Demographics and CU clinical characteristics

Sixty-one adult patients with CU were enrolled, 73.8% (n = 45) were female and 26.2% (n = 16) male. The median age of patients was 44.5 ± 14.9 years, ranging from 18 to 84 years old. Most patients (78.7%) had initiated CU symptoms less than 1 year before enrollment (Table 1).

Regarding the characterization of the CU type, 55.7% (n = 34) were diagnosed with CSU and 44.3% (n = 27) with CSU associated with ClndU as a comorbidity. The ClndU subtypes diagnosed in our population are shown in Table 1 (70.4% of patients were afflicted by more than one type of ClndU). Females accounted for 88.9% (n = 24/27) of ClndU patients, while only 61.8% of the CSU (n = 21 /34) were females (p = 0.021, Chi-Square Tests).

Thirty-four patients (55.7%) had at least one episode of angioedema within the last year. The presence of angioedema did not significantly associate with sex, age, recent onset of CU or the subtype of CU.

Table 1

ClndU subtypes in the study population. Please note that some patients present with several ClndU subtypes

ClndU subtypes	Number of patients
Delayed pressure urticaria	19.7% (n = 12)
Cholinergic urticaria	14.8% (n = 9)
Heat urticaria	14.8% (n = 9)
Symptomatic dermographism	13.1% (n = 8)
Cold urticaria	4.9% (n = 3)
Contact urticaria	4.9% (n = 3)
Solar urticaria	1.6% (n = 1)
Aquagenic urticaria	1.6% (n = 1)

Comorbidities

The frequency of comorbid atopic diseases was: asthma in 21.3% (n = 13), rhinitis in 29.5% (n = 18) and the combination of the two diseases in 32.8% (n = 20). Medically-confirmed psychiatric disorders (depression and / or anxiety disorder) were present in 78.7% (n = 48). Other comorbidities, such as arterial hypertension, type 2 diabetes and obesity were present in 31.2% (n = 19). The demographics and comorbidities presented in the study population are shown in Table 2.

Table 2
Demographics and medical history of the patients included. Please note that some patients present several comorbidities.

Variable	Population cohort (n = 61)
<i>Age</i>	
Median, years (min, max)	44.5 (18, 84)
<i>Gender</i>	
Women	73.8% (n = 45)
<i>Years since urticaria diagnosis</i>	
< 1 year	78.7% (n = 48)
2–5 years	9.8% (n = 6)
6–10 years	8.2% (n = 5)
> 10 years	3.2% (n = 2)
<i>Comorbidities</i>	
Allergic diseases	
Asthma and Rhinitis	32.8% (n = 20)
Rhinitis	29.5% (n = 18)
Asthma	21.3% (n = 13)
Food allergy	3.3% (n = 2)
Atopic dermatitis	1.64% (n = 1)
Cardiometabolic	
Arterial hypertension	19.7% (n = 12)
Diabetes	6.6% (n = 4)
Obesity	4.9% (n = 3)
Psychiatric disease	
Depression and/or anxiety disorder	78.7% (n = 48)

Diagnostic work-up

Complementary diagnostic tests were performed in more severe cases, according to the local follow-up protocols. Evidence for autoimmunity (positive anti-thyroid peroxidase antibodies, anti-nuclear antibodies or autologous serum test) was found in 38.8% (n = 19) of 49 tested patients. Autoimmune thyroid disease was evaluated in 68.9% (n = 42) of the patients and was present in seven patients (7/42 = 16.7%). Anti-

nuclear antibody (ANAs) assay was performed in 68.9% (n = 42), and positive in 14 patients (14/42 = 33.3%). The “dense fine speckled” was the most frequent (n = 10), followed by the “nucleolar pattern” (n = 4). C-reactive protein (CRP) was evaluated in 47.5% (n = 29) of patients. CRP was high in six patients (6/29 = 20.7%) and half of these also had positive antinuclear antibodies. None of the patients had abnormal erythrocyte sedimentation rate values.

The autologous serum test (AutoST) was performed in 9.8% (n = 8) patients with suspected diagnosis of autoimmune urticaria. Only one patient (out of 8) had a positive AutoST. This patient had been diagnosed with CU less than 1 year before enrolment and had a severe presentation of the disease, only partially controlled with the four antihistamines/day and omalizumab, and with frequent job absenteeism due to CU. The patient was also positive for ANAs but negative for autoimmune thyroid antibodies. Skin biopsy was performed in 9.8% (n = 6) of the patients, but none showed specific changes other than urticaria in histology.

Treatment

All patients were on first-line therapy with non-sedating H1 antihistamines at the time of enrollment, with the majority of the patients receiving a twice-a-day regimen (52.4%, n = 32, Table 3). Among those treated with omalizumab (n = 5), four had CSU and one had several subtypes of ClndU, namely cholinergic urticaria, pressure urticaria and symptomatic dermographism. Atopy was present in 75.0% (n = 6) of patients receiving montelukast therapy as additional therapy, resulting in an improvement of CU control with its introduction.

One patient was treated with ciclosporin after therapeutic failure with omalizumab. This was a 45-year-old female patient, with obesity and arterial hypertension, with CSU associated with angioedema diagnosis < 1 year before enrolment and presenting poorly controlled CU and angioedema despite medication with cetirizine four times a day (40 mg). Three patients were enrolled during acute exacerbations and were under treatment with systemic corticosteroid therapy as additional therapy at the time of assessment.

Table 3
Active treatment at enrolment in the study population.

Variable	Population cohort (n = 61)
<i>Treatment</i>	
Non-sedative H1-antihistamines	100% (n = 61)
Number of daily doses	
4	14.8% (n = 9)
3	13.1% (n = 8)
2	52.4% (n = 32)
1	19.7% (n = 12)
Montelukast	
Yes	13.1% n = 8
Omalizumab	
Yes	6.6% (n = 4)
Systemic corticotherapy	
Yes	4.9% (n = 3)
Ciclosporine	
Yes	1.6% (n = 1)

Clinical exacerbations and disease control

Disease status was evaluated using two outcomes: significant exacerbations and activity/disease control scores (UAS7 and UCT). Significant exacerbations of CU were defined by the need of unscheduled medical consultations, emergency room, hospitalization or job absenteeism. Forty-six patients (75.4%) had at least one significant exacerbation during the previous year. The median number of visits to the Emergency Department (ED) was one visit/patient/year, with the majority of patients (45.9%, n = 28) presenting with one or two ED episodes in one year, and a maximum value of four visits in one year. Hospitalizations due to CU exacerbation occurred in 8.2% (n = 5) of the patients, and four of these patients had both CU and angioedema presentation for less than 1 year. Unplanned consultations were needed in about half of the population and job absenteeism occurred in 14.8% (n = 9) of patients, with a maximum of 90 days and a minimum of 1 day (Table 4).

Table 4
 CU exacerbations (ED episodes, hospitalizations, unplanned consultations and job absenteeism)

Variable	Population cohort (n = 61)
<i>CU exacerbations</i>	75.4% (n = 46)
Visits to the Emergency Department	
> 3	9.8% (n = 6)
1–2	45.9% (n = 28)
0	44.3% (n = 27)
Hospitalizations	
2	3.3% (n = 2)
1	4.9% (n = 3)
0	91.8% (n = 56)
Unplanned consultations	
> 7	4.9% (n = 3)
5–7	8.2% (n = 5)
3–4	19.7% (n = 12)
1–2	19.7% (n = 12)
0	47.5% (n = 29)
Job absenteeism	
Yes	14.8% (n = 9)

The number of exacerbations correlated with higher UAS7 symptom scores ($p = 0.006$, Spearman correlation). In our sample, patients with CInDU had worst disease control scores (UAS7 and UCT questionnaires) when compared to patients with CSU only ($p = 0.022$, Mann-Whitney test). However, CInDU patients had fewer exacerbations requiring medical observation or hospitalization ($p = 0.015$, Mann-Whitney test).

A high number of antihistamines, use of corticosteroid therapy and/or ciclosporin for disease control correlated with higher UAS7 scores ($p = 0.006$, Spearman correlation) but no significant correlation was observed with the UCT score. The presence of angioedema associated with a higher number of exacerbations ($p = 0.022$, Mann-Whitney test) but with no differences concerning disease control (UAS7 and UCT), or the number of antihistamines used. Atopy (asthma, allergic rhinitis, food allergy and atopic dermatitis) and autoimmunity (positive antithyroid peroxidase antibodies, ANAs and / or AutoST) did not

significantly associate with the symptom scores or exacerbations. No other statistically significant associations were observed in relation to other variables, namely, complementary diagnostic tests or the presence of comorbidities.

Discussion

We presented new epidemiological data on refractory CU and looked for clinical factors associating with worse outcomes (exacerbations and symptom control).

Similar to other studies in Portugal and other countries(25, 26, 31, 32), more than 70% of the patients were female and the median age was around 45 years old. CSU represented more than 55% of all cases of CU, however, a wide variability has been found(32–34). Although the predominance of female patients was evident in the two groups of CU, CSU and ClndU, patients with ClndU had a higher predominance of females compared to CSU. This does not corroborate the literature, which indicates the absence of significant gender differences in ClndU compared to other types of urticaria(35).

Patients with exacerbations requiring unplanned consultations, emergency visits or hospitalization were mainly patients with a shorter course of disease (< 1 year). According to the literature, ClndU treatment is mainly symptomatic with avoidance of eliciting triggers(35). Thus, most of our exacerbating population also corresponds to patients with CSU whose trigger has not been identified, resulting in a more challenging symptom control.

The use of 2nd generation H1 antihistamines was observed in the whole sample, as recommended by current urticaria guidelines(2), contrarily to other studies in which the therapy was not totally in agreement with those suggested by the guidelines(25). The number of patients undergoing third-line therapy with omalizumab, ciclosporine and montelukast was 29.5% (n = 18), which differed from other series, with a higher value.(25).

In our sample, the use of severity and therapeutic monitoring scores - UAS7 and UCT - presented unequal accuracy, with UAS7 better associating with the occurrence of exacerbations and treatment dosis, emphasizing the recommended routine use of the UAS7 score has an important therapeutic value for the daily monitoring of patients. It is important to highlight that angioedema is not part of the UAS7 questionnaire.

Autoimmunity has been implicated in CU, resulting in the activation of systemic inflammatory processes that have implications in the evolution and control of the disease. High levels of CRP have been related to the presence of a systemic inflammatory process of autoimmunity in CU and, therefore, to disease activity(36). Takahagi et al. study demonstrated that high levels of CRP correlated with disease activity(37). Our work also found the presence of a group of patients with high CRP values, half of which also had positive antinuclear antibodies, demonstrating the importance of evaluating this parameter as a possible predictor of poor control and relationship with autominuity.

Regarding our data, it appears that the presence of angioedema may indicate a possible predictor of poor disease control, making the choice of treatment crucial for its control. Sussman et al considered that the presence of angioedema in CU is underreported and that it seems to be associated with an important negative impact, namely in the quality of life in daily activities and work performance, compared with patients who have CU without angioedema(38).

It is known that the prevalence of psychiatric disorders are evident in CU, however there are limited studies on their association with CU severity(39). The present study in patients with refractory CU showed an overwhelming prevalence of psychiatric disorders (depression and / or anxiety), highlighting the potential for predicting poor disease control and the need for a multidisciplinary approach in these patients.

Conclusions

Despite having some limitations, namely in its retrospective nature and unicentric character, several conclusions could be drawn in our work: (1) CSU alone was more frequent than ClndU; (2) the symptomatic uncontrolled group with more exacerbations included patients with a more recent diagnosis (< 1 year), highlighting the need for rapid therapeutic control at an early stage of the disease; (3) angioedema correlates with a higher number of exacerbations and its presence was superior when compared to other series(25); (4) UAS7 and UCT presented unequal accuracy, with UAS7 better associating with the occurrence of exacerbations and treatment dosis and (5) accurate diagnostic tests, namely autoimmune parameters and inflammatory markers, should be recommended in some individual cases.

It is important for the growing knowledge and uniform management of CU the use of guidelines for diagnostic and therapeutic approaches. With this uniformity and with a characterization by phenotypes, it will be possible to identify predictors of therapeutic response in order to contribute for better and personalized strategies to control this disease.

List Of Abbreviations

ANA - Anti-nuclear antibody

AutoST - Autologous serum test

CRP - C-reactive protein

CU - Chronic urticaria

CSU - Chronic spontaneous urticaria

ClndU - Chronic inducible urticaria

ED - Emergency department

NSAIDS - Nonsteroidal anti-inflammatory drugs

Declarations

This manuscript is original and its content has not been published or accepted elsewhere.

Ethics approval and consent to participate

The research was performed according to the Declaration of Helsinki of the World Medical Association. The study was approved by the local ethics committee. Patients provided written informed consent before enrolment. The anonymity of all the participants of this work was maintained during data analysis.

Consent for publication

All authors agree with the publication.

Availability of data and materials

Not applicable

Competing interests

Not applicable

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Author's contributions

IAC and FSR analysed and interpreted the data, and wrote the manuscript with supervision from ATB. FSR, RAF, JSP and RG collected the data. CC contributed in the statistical analysis of the data. ATB designed the study, interpreted the data and supervised manuscript preparation.

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Authors' information (optional)

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