

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 refractory 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 45.2% (n=19) of 42 tested patients. High C-reactive protein was present in 14.3% (n=6) of 42 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 half of the 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 dosis. 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(1,2). This definition excludes other medical conditions in which urticaria, 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).

CU is a common disorder, with a lifetime estimated prevalence of up to 1 percent of the general population in the United States, 7.8% in Germany, 9.0% in Southwest Norway and 3.4% in Portugal(2,5–

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(5,9).

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 dermatographism, 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 evaluation of some specific factors that aggravate CSU in a substantial subset of patients, 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)(2,10–20).

Routine laboratory tests seldom reveal abnormalities when the medical history does not suggest an underlying allergic etiology or the presence of systemic disease(2,21). 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(2,14,22).

The concept that CSU could represent an autoimmune disorder arose from the recognition that thyroid dysfunction and thyroid autoantibodies are more prevalent in patients with CSU. Antinuclear antibodies (ANAs) are also more prevalent in patients with CU than in the general population(9). Consequently, the presence of autoantibodies can be investigated upon clinical suspicion by the autologous serum skin test (AutoST) or other markers such as antinuclear antibodies (ANA) or antithyroid antibodies(23).

Autoimmunity and autoallergy, due to IgG and/or IgE autoantibodies, has been proposed as an etiology of CSU(24). It was proposed that an autoantibody or other histamine release factor could be present in the serum of these patients (especially those who had positive autologous serum skin test), namely human IgG directed against the IgE receptor alpha subunit (anti-Fc-epsilon-R1-alpha) and human IgG directed against the region IgE Fc (anti-IgE)(25). Although the presence of these autoantibodies can be demonstrated, their availability is still scarce, and, currently, its clinical utility is not well established. Skin biopsy may be performed to exclude 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(26). Histology findings can also predict the response to treatment. The presentation of a neutrophil pattern in histology has been associated to refractory chronic urticaria(27).

The EAACI / GA²LEN / EDF / WAO International Urticaria Directive recommends second generation H1-antihistamines (H1-AH) in standard dose therapy, however, treatment with H1-antihistamine leads to the

absence symptoms in less than 50% of patients(28). 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(29). Regarding control medications, 17.4% of the patients were not following guideline recommended CU treatment(29). A similar AWARE study was conducted in Portugal and included 76 patients(30). It showed that both wheals and angioedema independently affect chronic urticaria quality of life questionnaire (CU-QoL)(30). Guideline recommended non-sedative H1-AH treatment was used in almost 91.0% of patients at enrollment(30). 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(29).

There is a growing need for standardization of biomarkers to assess the severity and activity of CU and improve response to treatment. The objectives of our study were: (1) to characterize the clinical features, subtypes, cofactors, treatment and disease control status in adult refractory 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(2,3)) refractory to approved doses of H1-AH treatment, 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, associated comorbidities, such as medically diagnosed psychiatric disorders, asthma and atopic diseases, as defined by the European Academy of Allergy and Clinical Immunology and Global Initiative for Asthma. Obesity was defined as a body mass index greater than 30kg/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)(31) and Urticaria Activity Score 7 (UAS7)(32).

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 evaluated, 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 CInDU as a comorbidity. The CInDU subtypes diagnosed in our population are shown in table 2 (70.4% of patients were afflicted by more than one type of CInDU and all had associated spontaneous urticaria). Females accounted for 88.9% (n=24/27) of CInDU 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.

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).

Table 1. Demographics and medical history of the patients included. Please note that some patients present several comorbidities.

| Variable | Population cohort (n = 61) |
|----------------------------------------|----------------------------|
| Age | |
| Median, years (min, max) | 44.5 (18, 84) |
| Gender | |
| Women | 73.8% (n=45) |
| Years since urticaria diagnosis | |
| <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) |
| Comorbidities | |
| 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) |
| Autoimmune diseases | |
| Autoimmune thyroid disease | 11.5% (n=7) |
| Psoriatic arthritis | 1.64% (n=1) |
| Cardiometabolic | |
| Arterial hypertension | 19.7% (n=12) |
| Diabetes | 6.6% (n=4) |
| Obesity | 4.9% (n=3) |
| History of acute myocardial infarction | 1.64% (n=1) |
| Psychiatric disease | |
| Depression and/or anxiety disorder | 78.7% (n=48) |
| Malignant diseases | |
| Follicular thyroid tumor | 1.64% (n=1) |

Table 2. ClndU subtypes in the study population. Please note that some patients present with several ClndU subtypes

| ClndU subtypes | Number of patients |
|------------------------------------|--------------------|
| <i>Delayed pressure urticaria</i> | 19.7% (n=12) |
| <i>Cholinergic urticaria</i> | 14.8% (n=9) |
| <i>Heat urticaria</i> | 14.8% (n=9) |
| <i>Symptomatic dermatographism</i> | 13.1% (n=8) |
| <i>Cold urticaria</i> | 4.9% (n=3) |
| <i>Contact urticaria</i> | 4.9% (n=3) |
| <i>Solar urticaria</i> | 1.6% (n=1) |
| <i>Aquagenic urticaria</i> | 1.6% (n=1) |

Diagnostic work-up

Complementary diagnostic tests were performed in cases in which the clinical history suggests an underlying etiology, according to the local follow-up protocols, namely for patients with more severe presentation (UAS7 \geq 28 and/or UCT <12) or with longer evolution (>1 year).

Complementary tests performed for further classifying CU were complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), all performed in 68.9% (n=42), and the least frequent tests were skin biopsy, requested for only 6 patients. All patients evaluated had a CBC within the reference values; CRP was high in six patients (6/42 = 14.3%) and half of these also had ANAs⁺. In patients with high CRP results, infectious causes such as HSV, HBV, CMV, EBV and HIV were excluded. Regarding ESR testing (n=42), none of the patients presented abnormal values (1-20 mm / h).

Evidence for autoimmunity markers (positive anti-thyroid peroxidase antibodies, anti-nuclear antibodies or AutoST) was found in 45.2% (n=19) of 42 tested patients. Anti-nuclear antibody (ANAs) assay was positive in one third (n=14) of 42 tested patients. The "dense fine speckled" was the most frequent (n=10), followed by the "nucleolar pattern" (n=4). Routine measurement of thyroid stimulating hormone (TSH) has not been approved by international guidelines since 2018(2). Among patients who had ANAs⁺, 21.4% (n=3/14) had a diagnosis of autoimmune thyroid disease (ATID). The remaining 4 cases of ATID were ANAs⁻, corresponding to a total of seven patients (7/42 = 16.7%).

The 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 evaluation 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 ANAs⁺ but negative for autoimmune thyroid antibodies.

Skin biopsy was requested in patients with uncommon presentations, namely in painful lesions. Skin biopsy was performed in 9.8% (n=6) of the patients and five presented interstitial edema with a perivascular mixed infiltrate (lymphocytes, eosinophils, and in few neutrophils /basophils).

One patient presented vasculitic signs and hypocomplementemic urticarial vasculitis (*McDuffie* syndrome) was diagnosed. This was a 44-year-old female patient who presented urticaria with angioedema refractory to 4id antihistamine treatment, with about 1 year of evolution. She was submitted to a first skin biopsy due to painfull lesions, but no findings of vasculitis were found. Six months later, she started to present *Raynaud* phenomenon and developed echymotic papules. In this context, the skin biopsy was repeated on suspicion of vasculitis and the diagnosis of *McDuffie* syndrome was made. Histology showed the presence of slight angiocentric lymphohistiocytic infiltrate with the presence of some dispersed polymorphonuclear cells and also mild leukocytoclasia. Currently, she is under prednisolone 20mg/day plus bilastine 20mg/day with symptom control.

Urticaria with a predominance of neutrophils on histology was not found in any patient.

Treatment

All patients were on first-line therapy with non-sedating H1 antihistamines at the time of evaluation, with the majority of the patients receiving a twice-a-day regimen (52.4%, n = 32, Table 3). Among those treated with omalizumab (n = 4), four had CSU, one of them with autoimmune urticarial confirmed by AutoST⁺, and one had several subtypes of ClndU, namely cholinergic urticaria, pressure urticaria and symptomatic dermographism. Atopy was present in all patients receiving montelukast therapy as additional therapy, resulting in an improvement of CU control with its introduction, resulting in a reduction in the number of daily antihistamines to 1id in all cases. 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 and presenting poorly controlled CU and angioedema despite medication with cetirizine four times a day (40mg) and showing no clinical worsening of arterial hypertension at the time of data collection.

Three patients were evaluated during acute exacerbations and were under treatment with systemic corticosteroid therapy as additional therapy. The other patient who was medicated with systemic corticosteroid therapy was referred to the case of McDuffie syndrome. In association, this patient was medicated with one H1-AH per day.

Table 3. Active treatment at enrolment in the study population.

| Variable | Population cohort (n = 61) |
|---------------------------------------|----------------------------|
| <i>Treatment</i> | |
| <u>Non-sedative H1-antihistamines</u> | 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) |
| <u>Montelukast</u> | |
| Yes | 13.1% (n=8) |
| <u>Omalizumab</u> | |
| Yes | 6.6% (n=4) |
| <u>Systemic corticotherapy</u> | |
| Yes | 6.6% (n=4) |
| <u>Ciclosporine</u> | |
| 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) |
| <u>Visits to the Emergency Department</u> | |
| >3 | 9.8% (n=6) |
| 1-2 | 45.9% (n=28) |
| 0 | 44.3% (n=27) |
| <u>Hospitalizations</u> | |
| 2 | 3.3% (n=2) |
| 1 | 4.9% (n=3) |
| 0 | 91.8% (n=56) |
| <u>Unplanned consultations</u> | |
| >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=) |
| <u>Job absenteeism</u> | |
| 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 ClndU had worst disease control scores (UAS7 and UCT questionnaires) when compared to patients with CSU only ($p=0.022$, Mann-Whitney test). However, ClndU 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 (allergic 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 data on refractory CU and looked for clinical factors associating with worse outcomes (exacerbations and symptom control).

This study reflects the resources allocated to diagnose and treat patients with refractory chronic urticaria and describes the real-life scenario and clinical management in an urticaria center in a tertiary hospital. Similar to other studies in Portugal and other countries(29,30,33,34), 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(34–36). 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(37).

Despite delayed pressure urticaria is found to be a relatively rare form of physical urticaria in most case series(38), in our study it was present in a high number of patients (44.4% of ClndU, n=12/27). It appears immediately (within minutes) or, more commonly, 4 to 6 hours after a variety of pressure stimuli, which is not consistently recognised by the patients and clinicians. In our clinic, we routinely inquire the specific signs of the different triggers for all types of inducible urticaria, which is followed by the specific test to confirm the diagnosis.

Being a mast cell disease and potentially associated with a autoimmune disease, diagnoses of systemic autoimmune diseases and other mast cell disorders should be considered(39,40). Apparently, CU is associated with a specific pattern of comorbidities, including autoimmune, atopic and psychiatric diseases and there is no clear pattern in relation to malignant and cardiovascular diseases(41). In a Danish study by *Ghazanfar et al*, which evaluated the comorbidities of patients with CU in all centers in Denmark, over a 21-year period, atopic diseases were strongly overrepresented among patients(41). In our population, about one third of patients had at least one associated atopic disease. *Ghazanfar et al* also found a high prevalence anxiety/depression in the group of patients with CU, which is in line with the results of our work(41). Hypertension has been associated with a prolonged duration of CU(42), although other studies that examined the prevalence of cardiovascular diseases in populations with CU did not find an increased risk of these comorbidities compared to the general population(43). Our work showed a percentage of about 20.0% of patients who had a previous diagnosis of arterial hypertension. In this subgroup, with the exception of one patient who experienced therapeutic failure with omalizumab, the choice of treatment with cyclosporine was not considered by clinicians, speculating the consideration that its presence influenced the therapeutic choice. It is known that corticosteroids influence the glycemic profile, so it did not seem surprising that patients with a diagnosis of diabetes were not on corticosteroid therapy. Of the 61 patients evaluated at our center, only one patient was submitted to chronic corticosteroid therapy due to a a diagnosis of *McDuffie* syndrome.

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(29). The number of patients undergoing third-line

therapy with omalizumab, ciclosporine and montelukast was 21.3% (n = 13), which differed from other series, with a higher value(29).

CBC, ESR and CRP were requested for most patients, which is in line with European and recommendations. 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(44). *Takahagi et al.* demonstrated that high levels of CRP correlated with disease activity(45). 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 autoimmunity.

Autoimmune urticaria is implicated as a cause of CU in about 30% to 50% of idiopathic cases(46). In autoimmune urticaria, the involvement of autoantibodies causing histamine release after reaction with immunoglobulin E (IgE) epitopes or with the high affinity IgE receptor chain (Fc RI) receptors, should be considered, especially in AutoST⁺(2,46). Due to the lack of access to these methodologies in our hospital at the time of data collection, this complementary method had not yet been carried out.

ANAs are a group of autoantibodies directed against nucleus antigens and are found in many patients with autoimmune diseases. These autoimmunity markers are positive in patients with CU by approximately 15-29%(41,45). The detection of ANAs in serum has been carried out for several years to screening for autoimmune diseases, but this analysis lacks some degree of subjectivity. While it may be important to acknowledge the presence of these autoimmune markers to understand the CU mechanism, its role is not fully explained, neither its research criteria fully defined. *Margen et al* published a study aimed at identifying clinical and laboratory attributes of patients with positive ANA and CU. One of the conclusions of the study was that this subgroup of patients (ANA⁺) was characterized by greater refractoriness to treatment with standard licensed doses of antihistamines, despite the fact that most patients do not have associated autoimmune disease(46). These results were consistent taking into account the small prevalence of autoimmune diseases in the general population (around 5-7%)(46). Our work showed an important percentage of ANA⁺ patients, however only a few cases were diagnosed with autoimmune diseases. These results speculate the need to standardize the measurement of these markers in all population with CU refractory to antihistamine therapy, reinforcing the need to avoid their arbitrary research.

Thyroid disease is the most commonly reported autoimmune disease in patients with CU(46). Approximately 5 to 34% of patients with CU have antithyroid antibodies and another 5 to 10% have clinically or biochemically confirmed thyroid disease(47). The association between AITD and CU is an unsolved mystery and the criteria for when to request this type of complementary study are not completely defined / clarified(48). Thus, the fact that not all patients in our population have undergone this complementary study is justified.

It is known that the prevalence of psychiatric disorders are evident in CU, however there are limited studies on their association with CU severity(49). 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. The high prevalence can also be justified by the fact that there is an important prevalence of these disorders in the Portuguese general population, according to the World Health in a 2015 data survey(50), where Portugal had an estimated prevalence of 5.7% for depression and 4.9% for anxiety. These comorbidities should not be neglected in patients with chronic diseases such as CU, with research being of crucial importance.

Although the level of evidence for the efficacy of treatment with leukotriene receptor anatagonists being low, the drug that has been showing better results was montelukast. It was found that at the data collection, patients who were treated with montelukast had atopy (asthma and / or rhinitis with positive tests for aeroallergens) and CU disease control.

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. 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(37). 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.

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(51).

Conclusions

This study involved a limited number of patients that were regularly observed at an Allergology and Clinical Immunology Department of a University Hospital. It was decided to make a multidisciplinary approach involving also psychiatrists and Internal Medicine specialists to better characterize refractory chronic urticaria. Patients were also submitted to a large number of complementary diagnostic tests to identify associated pathology. Despite having some limitations, namely in its retrospective nature, several conclusions could be drawn in our work: (1) CSU alone is frequent but CSU associated with ClndU as a comorbidity can affect almost half of the patients; (2) The CSU symptomatic group with more exacerbations can include patients with a recent diagnosis (<1 year); (3) Angioedema can often be

present and be correlated with an higher number of exacerbations (4) UAS7 and UCT presented unequal accuracy, with UAS7 better associating with the occurrence of exacerbations and treatment doses (5) Patients with refractory CU can be prone to psychiatric disorders, such as depression and / or anxiety and (6) accurate diagnostic tests, namely autoimmune parameters and inflammatory markers, should be recommended in some individual cases.

It is important to have a growing knowledge and a uniform management of refractory CU with its characterization by phenotypes, which make it possible to identify predictors of therapeutic response in order to contribute for better and personalized strategies to control this disease.

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

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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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Abbreviations

ANA - Anti-nuclear antibody

AutoST - Autologous serum test

CBC - Complete blood count

CMV - Cytomegalovirus infection

CRP - C-reactive protein

CU - Chronic urticaria

CSU - Chronic spontaneous urticaria

CIIndU - Chronic inducible urticarial

EBV – Epstein–Barr virus infection

ED - Emergency department

HBV - Hepatitis B infection

HIV - Human immunodeficiency virus infection

HSV – Herpes simplex virus infection

NSAIDS - Nonsteroidal anti-inflammatory drugs

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