Clinical Features of Chronic Spontaneous Urticaria that Predict Disease Prognosis and Refractoriness to Standard Treatment

Laia CURTO-BARREDO1, Laura RIBA ARCHILLA2, Guillem ROURA VIVES2, Ramon M. PUJO1 and Ana M. GIMÉNEZ-ARNAU1
1Department of Dermatology, Hospital del Mar, Parc de Salut Mar, Departament de Medicina de la UAB, Universitat Autònoma de Barcelona, and 2Adknoma Health Research, Barcelona, Spain

Clinical spontaneous urticaria (CSU) is characterized by heterogeneous activity, evolution, associated comorbidities and response to treatment. The aim of this study was to identify prognostic factors in patients with CSU that predict disease course and response to standard treatments. An observational retrospective study was conducted in a cohort of 549 patients with CSU, comparing patients with isolated CSU and those with CSU with concomitant inducible urticaria (CSU-CIndU). The factors associated with a worse prognosis in terms of duration and/or CSU activity and its episodes were: multiple episodes of CSU (19.2% had more than one lifetime episode of CSU), late-onset (63.6% of patients developed first onset of CSU after the age of 45 years), concomitant CIndU (20.2%) and functional serum autoreactivity. Patients with CSU-CIndU required more frequent therapy after 5 years and higher doses of 2nd-generation H1-antihistamines. Of patients with a baseline Urticaria Activity Score 7 (UAS7) between 16 and 42, 84.6% required cyclosporin or omalizumab to achieve symptom control, compared with 15.4% of patients with a baseline UAS7 between 0 and 15 (p = 0.0013). Baseline CSU activity is the only factor found to be predictive for refractoriness to treatment with H1-antihistamines.

Key words: chronic spontaneous urticaria; disease activity; prognosis; serum autoreactivity; antihistamine refractoriness.

Accepted Apr 12, 2018; Epub ahead of print Apr 12, 2018

Corr: Ana M. Giménez-Arnau, Department of Dermatology, Hospital del Mar, Parc de Salut Mar, Departament de Medicina de la UAB, Universitat Autònoma de Barcelona, ES-08003 Barcelona, Spain, E-mail: anamariagi-menezarnau@gmail.com, 22505 Saga@gmail.com

Chronic urticaria (CU) is a condition characterized by wheals, angioedema or both, lasting for more than 6 weeks, and sometimes persisting for years. Spontaneous CU (CSU) has unpredictable symptoms, while inducible CU (CIndU) is provoked by, for example, cold, heat, pressure, friction, or contact e.g with proteins, among other factors. Both types can be present concomitantly. The prevalence of CSU in the general population ranges between 0.5% and 1% (1–4). CSU has a significant negative impact on patients’ quality of life, and is a considerable social and healthcare burden (5–7). Some clinical and laboratory parameters have been suggested to be predictive of more persistent and treatment-resistant CSU (4, 8). Autoimmunity may be involved in CSU with higher activity and longer duration (9–14). However, the significance of such observations is controversial (15).

The aim of this study was to identify specific demographic and phenotypic features in a large cohort of patients with CSU that may help to define prognostic factors, and predict disease course and the response to standard treatments, especially H1-antihistamines. The recognition of distinctive characteristics in the patients treated in our clinics would be of value in our daily practice.

MATERIALS AND METHODS

Study design and patient population

This observational study retrospectively reviewed the medical records of 1,056 patients who were registered with the Urticaria Unit of the Hospital del Mar, Barcelona, Spain, from 2001 to 2014. From a total of 997 patients aged over 16 years with a diagnosis of urticaria (acute urticaria, CSU or CIndU), data for 549 patients with CSU were included in the statistical analysis. Clinical features (Table S1†), laboratory parameters and extended complementary studies (Table SII†), prescribed drugs, response to treatment and evolution data were systematically entered in an electronic case-report form (www.adknoma.com/URTICARIA/login.aspx). CSU features involving activity, diagnostic tools, complementary exploratory tests, comorbidities and therapeutic recommendations were assessed according the EAACI/GA²LEN/
WAO/EDF guideline recommendations (1, 2). Serum autoreactivity was tested with the Autologous Serum Skin Test (ASST), Autologous Plasma Skin Test (APST) and Basophil Activation Test (BAT) through CD63 expression (9, 16, 17). Tables SII and SIII list the variables recorded in the electronic case-report form (1–3, 9, 18, 19). The Clinical Research-Ethics Committee (CREC) from the Hospital del Mar granted ethical approval for the study (2013/5363/I).

Statistical analysis

Descriptive statistics are provided for all CSU variables. Data for patients with isolated CSU (is-CSU) and patients with concomitant CIndU (CSU-CIndU) were compared. Quantitative variables were described using means and standard deviations (SD), and categorical variables using absolute and relative frequencies. Variables were compared between groups using non parametric Mann-Whitney or Kruskal-Wallis test for quantitative variables. Multivariate analysis was also performed using a bimodal logistic regression model adjusting for all factors (Table SIII).

RESULTS

Chronic spontaneous urticaria features that impact on prognosis and management

Relevant demographic features. The interval between the first CSU symptom and the baseline visit to the specialized urticaria centre was 4.2 ± 6.8 years (mean ± standard deviation (SD)) (n = 549), revealing a delay in establishing the correct treatment in some patients. Of the total 549 patients, 402 (73%) were female, the mean age at baseline visit was 51.5 ± 15.9 years, and mean age of onset of symptoms 47.3 ± 16.2 years. It is notable that 63.6% (314/494) of patients with CSU were > 45 years of age at the time of first episode of CSU. Of these patients, 74.5% had had urticaria continuously for more than 3 years; a higher percentage compared with the 60% of patients < 45 years of age at first episode of CSU (p = 0.0174).

Patients with the is-CSU form had had more recurrences than those with is-CSU, but the difference was not statistically significant (49.3 ± 15.4 vs. 52.0 ± 15.9 years; p = 0.0564).

Table II. Summary table showing the main characteristics of chronic spontaneous urticaria (CSU) related to worse prognosis of the disease in terms of duration and activity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Longer disease</th>
<th>Higher activity of the disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset CSU (&gt; 45 years)</td>
<td>Functional autoreactive serum (ASST+/CD63+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSU-CIndU</td>
<td>CSU-CIndU</td>
<td>Multiple episodes, relapsing CSU</td>
<td></td>
</tr>
</tbody>
</table>

ASST: Autologous Serum Skin Test; CSU-CIndU: CSU with concomitant inducible urticaria.

Of 549 patients with CSU, 438 (79.8%) had is-CSU and 111 (20.2%) CSU-CIndU, the most frequent CIndU associated was symptomatic dermographism (SyD) followed by delayed pressure urticaria (DPU) and cholinergic urticaria (ChU) (74.7%, 33.2% and 17.8% respectively; p < 0.0001). Patients with CSU-CIndU were younger than those with is-CSU, but the difference was not statistically significant (49.3 ± 15.4 vs. 52.0 ± 15.9 years; p = 0.0564).

The overall demographic and clinical characteristics of patients with CSU, is-CSU and CSU-CIndU are summarized in Table I.

Disease course. Almost 20.0% of patients had had more than one episode of CSU during their lifetime, with long periods completely free of symptoms: 5.8% of them had had more than 2 episodes, showing a longer course of CSU. Patients with the is-CSU form had had more recurrences than those with concomitant CIndU (27.0% vs. 17.1%; 0.0005).
Approximately 64% of patients with CSU still needed medical care after 1 year, but this percentage decreased to 32.4% and 17.3% by the 3rd and 5th years, respectively. After 5 years, 8.4% of patients were still visiting our department (Fig. 1). Patients with CSU-CIndU required more frequent therapy after 5 years of follow-up than patients with is-CSU (15.8% vs. 15.1%; p < 0.05). The Urticaria Activity Score the day before UAS3w (UAS3w was 1.9 ± 1.9, 64.1% patients (85/549) showed significantly higher UAS7 than patients with ASST+/CD63+ (26.57 ± 10.56 vs. 18.40 ± 12.05, p = 0.004) (16). With regard to the positivity of ASST or APST, no significant differences were found between is-CSU and CSU-CIndU patients (53.9% vs. 58.2%, p = 0.4939 and 45.7% vs. 47.4%, p = 0.8229, respectively) (Table II).

Management and therapeutic control of chronic spontaneous urticaria

Prior to the baseline visit, 88.2% (484/549) of patients had been treated for urticaria. A licensed dose of 2nd-generation H1-antihistamines was the most frequently prescribed first-step treatment, followed by a combination of 1st- and 2nd-generation H1-antihistamines (27.0% and 19.3%, respectively). A further 18.7% had been previously treated with high doses of 1st-generation H1-antihistamines, and 8.8% had been treated exclusively with 1st-generation H1-antihistamines, which is not a recommended practice due to frequent adverse events (1, 2).

Patients with CSU were treated according to the current published guidelines (1, 2, 19, 21). In our series,
Refractoriness to treatment was analysed when 1st- and 2nd-generation H1-antihistamines were used in monotherapy or combined (Fig. 2). Most of the patients treated with licensed doses of 1st-generation H1-antihistamines were refractory to treatment (73/80, 91%). Some of the refractory patients (21/73, 28.8%) received 4-fold doses of 1st-generation H1-antihistamines, but 95% of them remained refractory. With 2nd-generation H1-antihistamines, the rates of refractoriness were lower. Even so, 78% of patients were refractory to licensed doses (332/427) and of those who received 4-fold 2nd-generation H1-antihistamine doses (181/332), 77% still had wheals and/or angioedema. No advantages were seen in treatment with a combination of 1st- and 2nd-generation H1-antihistamines.

Multivariate analysis including 42 variables (Table SIII) was performed to assess factors potentially involved in refractoriness to any H1-antihistamine at any dose. Only baseline UAS7 appeared to be useful to predict refractoriness to H1-antihistamine. The mean baseline UAS7 was 15.1 ± 12.0 in well-controlled patients on first-line treatments, 21.8 ± 11.8 in patients controlled with second-line treatments, and 29.5 ± 11.1 in patients who required third-line treatments to achieve disease control (p < 0.0001). According to the UAS7, 84.6% of patients with a baseline UAS7 between 16 and 42 required cyclosporine or omalizumab to achieve symptom control, in contrast to 15.4% of patients with a baseline UAS7 between 0 and 15 (p = 0.0013) (Fig. 3).

**DISCUSSION**

CSU is not a rare disease, but there is often a significant delay in accurate diagnosis. In this analysis the time for patients to get specialized attendance was more than 4 years. This fact highlights the need to train general practitioners and emergency units in the initial identification and treatment of the disease, so that they can provide the correct information about the disease, and suggest complementary explorations and specialized management. A correct initial approach is crucial, because 5 years after disease onset at least 8.4% of patients with CSU (46/549) had experienced hives and itch, requiring...
healthcare. This data is in agreement with the percentage described by Gaig et al., which showed 11.3% of patients with CSU were symptomatic for more than 5 years (22). Even longer symptomatic periods have been described (4, 8, 23).

As described previously, all types of urticaria are more common in females than males (4, 22). Some distinctive findings were helpful to define potential prognostic factors and establish a therapeutic plan. Although classically CSU occurs mostly at 20–40 years of age (24–28), in the current series the mean age of patients was higher (47.3 ± 16.2 years). Twenty-two percent of cases in our series were 65 years of age or older at the onset of CSU. CSU episodes were longer with worse prognosis when they started at or over the age of 45 years, requiring effective and safe treatments for a longer period.

Of the 549 patients with CSU, 19.2% had had more than one episode. This particular phenotype of patients prone to CSU has shorter episodes, but a longer duration of complete disease than patients who have a single episode of CSU.

These results suggest an underestimation of angioedema (16.2% of patients with CSU in the current study). This could be partially explained because this type of data was not recorded in their medical records. This finding is consistent with the results of the ASSURE study, in which angioedema was reported more frequently by patients than by physicians (28, 29). Nevertheless, in our series angioedema did not correlate with a worse prognosis in terms of high activity, longer duration or antihistamine refractoriness of the disease; however, these results should be interpreted with caution since the current sample size is very small ($n = 83$).

Concomitant subtypes of urticaria in CSU vary from 10% to 50% depending on the series (25–27, 30, 31). Of CSU-CIndU patients, 20.2% showed more active and longer episodes of CSU. CSU patients with CIndU were also the most frequently treated after 5 years of follow-up. Furthermore, they required higher doses of 2nd-generation H1-antihistamines to control the disease. This is consistent with Kozel et al. (25); in a series of 220 patients with CSU only 20.8% of patients with the CSU-CIndU subtype were symptom-free after 1 year of treatment compared with 47.4% of patients with is-CSU. Patients with CSU-CIndU showed a significantly lower number of episodes and longer periods with active disease compared with patients with is-CSU in the current study.

More than half of the patients in this series had a positive ASST result (14). Patients with positive ASST and positive CD63 expression showed significantly higher UAS7 (16), in concordance with previous studies (32, 33).

Some complementary exploratory tests need careful interpretation regarding their relationship with disease activity and prognosis. Serum levels of D-dimer tended to be high in patients with more active CSU refractory to anti H1-antihistamines, but the sample size makes this result inconclusive. Significantly high levels of sALP were found with no other associated diseases. A possible relationship between this observation and vitamin D deficiency can be hypothesized (34–36). Vitamin D has recently been suggested to play a role in the pathogenesis of more active and longer-lasting cases of CSU (37–39). However, no clear-cut relationship was found in our study between sALP levels and UAS7.

The use of a licenced dose of 2nd-generation H1-antihistamines and an increased dose is recommended in current urticaria guidelines (1, 2). Nevertheless, looking at data for the heterogeneous treatments prescribed prior to the baseline consultation in our department, it is clear that, in practice, the guidelines are not followed completely (1–3, 40). Although 1st-generation H1-antihistamines, and the combination of antihistamines, are no longer recommended (1, 2), almost 20% of patients were treated previously with this combination. These patients showed higher percentages of refractoriness to the treatment compared with patients treated with 2nd-generation H1-antihistamines, at licensed and increased doses. Thus, we agree with and support the European guidelines that 1st-generation H1-antihistamines and the combination of 1st and 2nd-generation H1-antihistamines should not be used in treatment of CSU.

It is important to note that 77.7% of patients with CSU in our series were symptomatic despite the use of licensed doses of 2nd-generation H1-antihistamines. Although it has been reported that 63.2% of patients who are non-respondent to licensed doses of H1-antihistamines can benefit from increased doses, immunomodulation was required quite frequently in our series (41).

Baseline UAS7 has been shown to be the only parameter able to predict refractoriness to H1-antihistamines. Almost 90% of patients with CSU with a baseline UAS7 >16 needed CyA or omalizumab combined with antihistamines in order to control their symptoms.

Despite some limitations based on the retrospective and single-centre character of this study, we conclude that the following factors indicate the worst prognosis, in terms of duration and/or activity of the disease and its episodes: multiple episodes of CSU; late-onset; concomitant CIndU; and functional serum autoreactivity. We recommend the routine use of validated patient-reported outcomes, such as the UAS7, as this has a predictive therapeutic value that will be of use in daily clinical practice.

**ACKNOWLEDGEMENTS**

This paper is based on a research project supported by Novartis Grant. The authors thank Mariana Lacentra for work as data manager and Monica Giménez for assistance in drafting the manuscript. **Funding sources.** Novartis grant.
**Conflicts of interest.** AMG-A is a medical advisor for Uriaich Pharma, Genentech and Novartis. She has received research grants from Intendis-Bayer, Uriaich Pharma and Novartis, and has participated in educational activities sponsored by Uriaich Pharma, Novartis, Genentech, Menarini, Glaxo Smith & Kline, Merck MSD, Almirall and Leo Pharma. The other authors declare no conflicts of interests.

**REFERENCES**


34. Nawawi H, Girgis SI. Serum levels of bone-specific alkaline phosphatase and procollagen type I carboxyterminal peptide