Angioedema severity and impacts on quality of life: chronic histaminergic angioedema versus chronic spontaneous urticaria

Marina Sabate-Bresco[1], Nuria Rodríguez-Garijo[1], JULIÁN AZOFRA[2], María L. Baeza[3], Carmen Diaz Donado[2], Pere Gaig[4], Mar Guilarte[3], Valeria Herrera-Lasso [4], Moises Labrador-Horrillo[3], Anna Sala-Cunill[3], Beatriz Veleiro[5], Pilar Gil[1], and Marta Ferrer[1]

[1]Clinica Universidad de Navarra
[2]Hospital Universitario Central de Asturias
[3]Instituto de Salud Carlos III
[4]Hospital Universitari de Tarragona Joan XXIII
[5]Complexo Hospitalario Universitario A Coruna

September 25, 2021

Abstract

Background: Chronic histaminergic angioedema (CHA) is defined as recurrent episodes of isolated angioedema (without hives) of unknown cause that respond to the same treatment as chronic spontaneous urticaria (CSU). Quality of life (QoL) studies have not been performed for CHA, except those carried out in the context of CSU associated with angioedema attacks (CSU-AE). Moreover, biomarkers for monitoring disease activity in CHA have not been identified. We aim to describe the burden of CHA and impact on patient QoL, compare the findings to those in CSU-AE patients, and investigate biomarker associations with disease severity and QoL parameters. **Methods:** We performed a prospective multicenter study that included 68 patients with CHA and 63 patients with CSU-AE. Demographic and clinical variables were collected. Validated patient-reported questionnaires were employed to analyze the quality of life and disease activity. Blood and serological parameters, including blood cell count, C-reactive protein, D-dimer and total IgE, were also analyzed. **Results:** Angioedema disease activity was significantly higher in CSU-AE patients (median AAS7, IQR: 1, [0–1]) than CHA patients (0, [0–1]; p= 0.022). A considerable impact on QoL was found in both groups, although significantly worse values were found for CSU-AE (median AEQoL, IQR: 37, [10–65]; p=0.005). CHA patients were older than CSU-AE patients, and female predominance was not observed. **Conclusions:** Angioedema severity and QoL impacts are significantly worse in CSU than in chronic histaminergic angioedema. Angioedema should be included in severity urticaria scores (UAS) as well as in specific quality of life urticaria scales.

Article type: Original article

Angioedema severity and impacts on quality of life: chronic histaminergic angioedema versus chronic spontaneous urticaria

Short title: Quality of life and severity related to angioedema

Nuria Rodríguez-Garijo, MD[1], Marina Sabaté-Brescó, PhD[2,3,4], Julián Azofra, MD, PhD[5], Maria Luisa Baeza, MD, PhD[6], Carmen Diaz Donado, MD, PhD[5], Pere Gaig, MD[7], Mar Guilarte, MD, PhD[4,8], Valeria Herrera-Lasso, MD[7], Moisés Labrador-Horrillo, MD, PhD[4,8], Anna Sala-Cunill, MD, PhD[4,8], Beatriz Veleiro MD, PhD[9], Maria Pilar Gil, MD, PhD[1], Marta Ferrer, MD, PhD[2,3,4]

[1]Department of Dermatology, Clinica Universidad de Navarra, Pamplona, Spain

[2]Department of Allergy and Clinical Immunology, Clinica Universidad de Navarra, Pamplona, Spain

[3]Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain

[4]RETIC de Asma, Reacciones Adversas y Alérgicas (ARADYAL), Spain

[5]Allergy Section, Hospital Universitario Central de Asturias, Oviedo, Spain

[6]Allergy Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain; Biomedical, Research Network on Rare Diseases (CIBERER)-U761, Madrid, Spain. Gregorio Marañón Health Research Institute, Madrid, Spain

[7]Allergy Section, Hospital Universitari Joan XXIII de Tarragona; Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Tarragona, Spain

[8]Allergy Section, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[9]Complexo Hospitalario Universitario de A Coruña, A Coruña, Spain

Corresponding author

Marta Ferrer Puga, mferrerp@unav.es

Telephone: +34 948 25 54 00

Clínica Universidad de Navarra

Av. Pio XII, 36

31008 Pamplona (SP)

Acknowledgments

This work was supported by grants #PI16/01304 and #PI20/01536 from the Instituto de Salud Carlos III (ISCIII) and the Thematic Networks for Co-operative Research Centres: ARADyAL network (RD16/0006/0031) from ISCIII, co-founded by Fondo Europeo de Desarrollo Regional (FEDER).

Conflict of interest statement

The authors have no conflicts of interest to disclose.

Manuscript word count: 2704 words

Abstract word count: 249

References: 35

Figures: 2

Tables: 2

Abstract

Background: Chronic histaminergic angioedema (CHA) is defined as recurrent episodes of isolated angioedema (without hives) of unknown cause that respond to the same treatment as chronic spontaneous urticaria (CSU). Quality of life (QoL) studies have not been performed for CHA, except those carried out in the context of CSU associated with angioedema attacks (CSU-AE). Moreover, biomarkers for monitoring disease activity in CHA have not been identified. We aim to describe the burden of CHA and impact on patient QoL, compare the findings to those in CSU-AE patients, and investigate biomarker associations with disease severity and QoL parameters.

Methods: We performed a prospective multicenter study that included 68 patients with CHA and 63 patients with CSU-AE. Demographic and clinical variables were collected. Validated patient-reported questionnaires

were employed to analyze the quality of life and disease activity. Blood and serological parameters, including blood cell count, C-reactive protein, D-dimer and total IgE, were also analyzed.

Results: Angioedema disease activity was significantly higher in CSU-AE patients (median AAS7, IQR: 1, [0–1]) than CHA patients (0, [0–1]; p= 0.022). A considerable impact on QoL was found in both groups, although significantly worse values were found for CSU-AE (median AEQoL, IQR: 37, [10–65]; p=0.005). CHA patients were older than CSU-AE patients, and female predominance was not observed.

Conclusions: Angioedema severity and QoL impacts are significantly worse in CSU than in chronic histaminergic angioedema. Angioedema should be included in severity urticaria scores (UAS) as well as in specific quality of life urticaria scales.

Keywords: Angioedema, Chronic Histaminergic Angioedema, Chronic Spontaneous Urticaria, Disease activity, Quality of Life

Introduction

Angioedema (AE) is defined as localized and self-limited swelling of the deep dermis and subcutaneous or submucosal tissues due to a rapid-onset increase in vascular permeability, causing local plasma extravasation secondary to the release of vasoactive mediators.[1,2]

According to the indicated vasoactive mediator, AE can be classified into two types: histamine-mediated AE (induced by mast cell activation and basophil degranulation) and bradykinin-mediated AE (due to excessive bradykinin), as observed in hereditary angioedema, acquired angioedema with C1 inhibitor deficiency (related to lymphoproliferative and autoimmune diseases) and angioedema related to angiotensin-converting enzyme (ACE) inhibitors.[3,4]

Histamine-mediated AE is the most frequent form of angioedema,[2] and it is classified as chronic histaminergic acquired angioedema (CHA) when allergies or other causes have been excluded and positive treatment responses to antihistamines, corticosteroids, adrenaline, or omalizumab[5] have been reported. Histamine-mediated AE can occur isolated as CHA or associated with wheals in chronic spontaneous urticaria (CSU). Classically, CSU is characterized by the presence of recurrent episodes of wheals (hives) with or without angioedema for at least 6 weeks.[6]Approximately 33–67% of all patients with CSU present with wheals and angioedema.[7] For this reason and because CHA responds to urticaria treatments, CHA is typically considered a subtype of CSU without wheals. However, a recent study[8] found several features that differentiate CHA from CSU, suggesting that CHA should be considered a separate entity.

Angioedema can be disfiguring, limit daily activities and have a significant impact on quality of life.[9,10] AE impacts on quality of life (QoL) have been largely explored in bradykinin-related AE[11,12]; however, specific QoL studies for CHA have not been performed, except for those carried out in the context of CSU associated with angioedema attacks.[13]

We previously reported differences in cellular activation and autoimmunity parameters between CHA and CSU[8] in the same cohort of patients. The aim of this study was to describe the burden of the disease and the impact on QoL in patients with CHA and compare the disease severity and quality of life of angioedema in patients suffering from chronic urticaria (CSU-AE).

Finally, due to a growing interest in identifying biomarkers to monitor disease activity and response to treatment, we selected several previously reported potential biomarkers for CSU activity[14-16] and assessed them in our study population as well as their relationship with disease activity and quality of life.

Materials and methods

Patients and clinical data

We performed a prospective study comparing 68 patients with CHA and 63 patients with CSU-AE who were recruited in 6 hospitals across Spain. All patients were older than 18 and provided signed informed consent

to participate in the study. Ethical approval was obtained in each of the collaborating centers, and the study followed Good Clinical Practice guidelines and the Helsinki Declaration.

The inclusion criterion to fulfill the diagnosis of CHA was the presence of recurrent AE that responds to treatment with antihistamines, corticosteroids, adrenaline or omalizumab. The exclusion criteria were the presence of bradykinergic AEs, ACE inhibitor intake, delayed-pressure AEs, vibratory AEs or edema induced by nonsteroidal anti-inflammatory drugs (NSAIDs). All patients had normal C1INH, C1q, C3 and C4 protein levels and normal C1INH activity.

We collected demographic features, and the patients were requested to complete validated patient-reported questionnaires. Disease activity was determined by the following questionnaires: Angioedema Activity Score for 7 consecutive days (AAS7) in both CHA and CSU-AE patients and Urticaria Activity Score over 7 Days (UAS7) in CSU-AE patients. The AAS7 score was categorized into four score levels: no episodes (0), low (1–6), moderate (7–18) and high (19–105).[17] UAS7 was also divided into four score bands: no episodes (0), low (1–6), moderate (7–27) and high (28–42).[18] The impact on quality of life was measured by the Angioedema Quality of Life (AE-QoL) in CHA and CSU-AE patients and by the Chronic Urticaria Quality of Life (CU-Q_2oL) questionnaires in CSU-AE patients.

In addition, we collected blood and serologic parameters in the clinical laboratories of each center: total serum IgE, blood cell counts, D-dimer and C-reactive protein (CRP).

Statistical analysis

Statistical analyses were performed using Stata (version 12.0; StataCorp, United States). Graphics were generated with GraphPad Prism 8 (GraphPad Software, United States). Qualitative variables are reported as the total number and percentage and were compared using chi-squared tests. Quantitative variables are reported as the mean with standard deviation or median with range and were compared using Student's t-test with Welch's correction (normally distributed) or the Mann–Whitney U test and Kruskal–Wallis test (nonnormally distributed). Spearman's correlation coefficient (r) is reported for correlations. To test for normality distribution, we applied the D'Agostino-Pearson test. Values were considered significant at $p<0.05$.

Results

A total of 131 patients were registered: 68 patients with CHA and 63 patients with CSU-AE. The characteristics of the patients are summarized in Table 1.

Demographic characteristics

As observed in Table 1 and as previously reported for this cohort,[8] significantly different gender and age distributions were observed between the two groups. The male/female ratio in CHA was 0.78, whereas that in CSU was 0.36. The proportion of women was significantly higher in CSU. The mean age was significantly higher in CHA.

Angioedema episodes and treatment

When patients were asked about the duration of angioedema episodes, the most common answers were 2–3 days in CHA (22.1%) and 24–48 hours in CSU-AE (27%). Although no significant differences were detected, we observed a trend for a longer duration of angioedema episodes in CHA. No significant differences in the number of angioedema episodes within the previous 12 months were found.

Overall, 69.12% of CHA patients and 82.54% of CSU-AE patients were taking medication to prevent those episodes. The number of patients who followed treatment with H1-antihistamines was significantly higher in CSU-AE (79.37%) than in CHA (52.94%, p=0.001). Additionally, updosing was more necessary in patients with CSU-AE (36.51%, p=0.015), and the number of patients who received fourfold the licensed dose was also higher in this group (9.52%, p=0.041). No significant differences in the other treatments (corticosteroid, omalizumab or others) were observed. However, the number of different concomitant treatments administered to the patients was significantly higher in CSU-AE.

Emergency department visits

The majority of patients needed at least one emergency department (ED) visit after their diagnosis, with 60.3% in CHA and 71.4% in CSU-AE. We did not find differences in the overall number of ED visits since the diagnosis. However, significant differences in the number of ED visits within the previous year were found, with a median of one visit in CHA patients and two visits in CSU-AE patients (p= 0.040).

Angioedema activity score

The details of the AAS7 questionnaire are shown in Table 2. We found significant differences in angioedema severity between the CHA and CSU-AE patients. The AAS7 score was significantly higher in CSU-AE (median, IQR: 1, [0–1]) than in CHA (median, IQR: 0, [0–1], p= 0.022).

In CHA, 58.1% of patients reported no AE episodes within the previous 7 days, 32.3% had low scores, 9.7% had moderate scores, and no patients had high scores. In CSU-AE, 42.3% of patients had no AE episodes in the past 7 days, 38.5% reported low scores, 11.5% had moderate scores and 7.7% had high scores. Only the CSU-AE patients had severe angioedema episodes in the AAS7 questionnaire (severe AAS7 range: 19–105) (p= 0.041).

Correlation with the Urticaria Activity Score

The median UAS7 score in CSU-AE was 3.75 (IQR: 0–17). Regarding the relation between AAS7 and UAS7 in the CSU-AE group, we found a significant association (p<0.001) with a strong positive correlation (Spearman's rho= 0.7206).

Quality of life

We found significant differences between the two groups regarding quality of life (Table 2). When comparing the AE-QoL questionnaire, quality of life was significantly lower in CSU-AE (median, IQR: 37 [10–65]) than in CHA (18 (4–40), p=0.005). Across all dimensions, the AEQoL scores were significantly higher (worse QoL) in CSU-AE. In both groups, the most affected dimension was fear/shame (38 [0–58] in CHA vs. 50 [21–79] in CSU-AE, p=0.031), followed by fatigue/mood (15 [0–40] in CHA vs. 35 (0–65) in CSU-AE, p=0.012), functioning (0 [0–19] in CHA vs. 25 (0–56) in CSU-AE, p< 0.001) and nutrition (0 [0–13] in CHA vs. 25 (0–50) in CSU-AE, p=0.007).

Across most dimensions, the mean AEQoL scores were generally higher among patients reporting a higher disease severity AAS7 score (Figure 1A and B). This finding is reflected in a moderate positive correlation between AAS7 and AE-QoL (Spearman's rho= 0.3892, p<0.001)

For CSU-AE, the median score of the CU-Q_2oL questionnaire in CSU-AE patients was 49 (IQR: 27–66). We found a very strong positive correlation between AE-QoL and CU-Q_2oL (Spearman's rho= 0.8809, p<0.001) and a moderate positive correlation between UAS7 and CU-Q_2oL (Spearman's rho= 0.5455, p=0.002).

Biomarkers

We assessed several biomarkers that have been proposed to be associated with CSU severity, such as CRP, D-dimer, basophil and eosinophil counts and total IgE. In CSU-AE patients, we observed a significant inverse correlation between UAS7 and eosinophil count (Spearman's rho= -0.3086, p=0.0392), while the other 4 parameters did not reach statistical significance, although a trend was observed for some of them (Figure 2A). For CSU-AE, no significant correlation was observed between AAS7 and any biomarker (Figure 2B), while in CHA, AAS7 showed a significant inverse correlation with D-dimer (Spearman's rho= -0.3007, p=0.0243), with no correlations observed with the rest of the biomarkers studied (Figure 2C).

We also assessed the QoL score correlations with the selected biomarkers. For CU-Q_2oL, moderately significant correlations were obtained for D-dimer (Spearman's rho= 0.4479, p=0.0005) and eosinophil counts (Spearman's rho= -0.3780, p=0.0034). In the case of CSU-AE, AE-QoL significantly correlated with the same biomarkers as CU-Q2oL, namely, D-dimer (Spearman's rho= 0.4636, p=0.0003) and eosinophil counts (Spearman's rho= -0.2867, p=0.0243). In CHA, AE-QoL did not present any significant correlations.

Discussion

Although considerable attention has been focused on hereditary angioedema because of its severity, little attention has been dedicated to mast cell-mediated angioedema. In the present work, we sought to depict the direct impact of angioedema in CSU and in CHA (isolated angioedema), by comparing the same angioedema severity and quality of life scales.

CSU has a significant impact on quality of life, and although itch is responsible for much of this effect, angioedema is also a key factor. In CSU, angioedema has been found to be associated with higher severity, longer duration and less response to therapeutic options. However, angioedema is underdiagnosed,[19] and it is not included among the most widely used severity scores, namely, UAS and UAS7, which only includes the number of hives and itch severity[20]; moreover, angioedema is frequently overlooked as an outcome in clinical trials, which mostly focus on the main variable, itch.[21,22] Some studies have shown the influence of angioedema in CSU and compared CSU patients with and without angioedema attacks.[19,23-29] However, the results are somewhat controversial, with certain studies indicating a lack of differences in disease activity[29] and other studies describing a greater severity in CSU with angioedema.[27] However, the disease severity and impacts on the quality of life of patients with CHA alone have not been clarified.

Our study compared CSU-AE and CHA for the first time and found differences in AAS values, suggesting a higher severity of CSU-AE. This finding appeared to be related to the fact that there were more CSU-AE patients in the severe level of the AAS7 questionnaire. Similar results were reported by Sussman et al.,[19] who found that more patients with CSU-AE had severe disease activity, as measured by the UAS, than those with CSU without angioedema attacks. However, one limitation of the results is the difficulty of differentiating hives, itch and angioedema when evaluating quality of life.

We indeed found that angioedema in the context of CSU is more severe and has a greater need for medication and emergency visits than angioedema with CHA; however, whether these differences are biased by the presence of hives and itch could not be determined. We also show that the AAS7 tool has a very good correlation with CSU severity; therefore, it might be useful to design a new urticaria activity score that incorporates AAS items. In that sense, the Urticaria Control Test (UCT) is more comprehensive because it includes swelling in the main control question: "How much have you suffered from the physical symptoms of urticaria (itch, hives (welts) and/or swelling) in the last four weeks?" However, UCT is not a severity score system.

A possible explanation for the differences is that angioedema present in CSU is produced when skin inflammation is more profound, thus paralleling a more severe disease. In contrast, CHA is a different and less severe entity that presents milder angioedema episodes.

We also confirm in this paper that both angioedema and urticaria quality of life scores correlate very well with disease severity. These questionnaires also help patients feel understood. With the available technology, better patient care will be achieved by sending these questionnaires prior to the clinical visit. In terms of the severity score, it might be very useful to incorporate the angioedema quality of life questionnaire into the CSU questionnaire.

Our observations also revealed the considerable impact on quality of life in CHA and CSU-AE patients. We observed marked emotional stress in both groups, and the most affected dimension in CSU-AE and in CHA was fear/shame followed by fatigue/mood. Furthermore, in both groups, patients with a higher frequency of attacks generally showed worse quality of life in the total AE-QoL score and its different dimensions.

Last, in recent years, many biomarkers for monitoring CSU have been described, most of which are related to disease activity, such as CRP, D-dimer, basophil and eosinophil counts or total IgE.[16] Several publications have reported that increased levels of CRP,[30] D-dimer[31]and total IgE[32] and decreased basophil counts[33] and eosinopenia[34] correlate with UAS7. In our study, we observed a significant inverse correlation between UAS7 and eosinophil count. Recently, similar results have been reported by Kolkhir et al.[34] who found that eosinopenia in patients with CSU was associated with high disease activity and poor treatment response.

A significant correlation was not observed among the rest of the biomarkers and UAS7, although a trend was shown, suggesting that significant results might have been obtained with a larger cohort, where more patients with high severity could be followed. Again, we did not find eosinopenia in the CHA group, thus indicating a different mechanism.

To date, biomarkers associated with histamine-mediated AE have not been identified. The presence of angioedema in CSU (compared to CSU without angioedema) has not been shown to be associated with altered levels of anti-FceRI, anti-IgE, substance P, B cell activation factor and tryptase,[15] which is consistent with them being two presentations of the same entity. However, CHA does seem to present differences in sex distribution and autoimmunity[8] or the presence of basopenia[8] or eosinopenia. It is very interesting that in this study, D-dimer was inversely correlated with CHA disease activity but not observed for CSU-AE patients.

We also assessed the QoL questionnaire correlations with biomarkers as an additional outcome related to disease severity. Patients with high severity scores in UAS7 have also been reported to have a poorer quality of life.[35] For CSU-AE, both QoL questionnaires depicted significant moderate correlations with D-dimer and eosinophil counts, with no correlation observed for CHA based on the AE-QoL. While not all previously published biomarkers could be confirmed in our cohort, severity and quality of life questionnaires in CSU-AE presented more correlations with some of the biomarkers compared to CHA.

In conclusion, in both isolated chronic angioedema and angioedema associated with hives in chronic spontaneous urticaria, mast cell-mediated angioedema has a significant impact on quality of life, which correlates with the disease severity, emergency department visits and rescue medication use. The quality of life and frequency of angioedema are greater in chronic spontaneous urticaria than in isolated chronic histaminergic angioedema.

Differences between CSU-AE and CHA indicate that they are different entities or at least differing phenotypes. We favor the former view. Nevertheless, angioedema deserves a better representation in chronic urticaria severity scores and quality of life questionnaires. It would be useful for experts designing such tools to highlight angioedema when it is associated with CSU so that questionnaires for angioedema alone can be employed for angioedema without urticaria.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Contributors

JA, MLB, CDC, PG, MG, VHL, MLH, ASC, BV and MFP equally contributed to study design. JA, MLB, CDC, PG, MG, VHL, MLH, ASC, BV and MFP contributed to participant recruitment for clinical performance assessment, and NRG, MSB, MPG and MFP performed the technical analysis. NRG and MSB organized data collection, analysis, and figure preparation. NRG, MSB, JA, MLB, CDC, PG, MG, VHL, MLH, ASC, BV, MPG and MFP contributed to the literature search and writing of the original draft of the manuscript or its critical revision.

References

1. Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol.* 2005;53(3):373-388.

2. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy.*2014;69(5):602-616.

3. Sala-Cunill A, Guilarte M. The role of mast cells mediators in angioedema without wheals. *Curr Treat Options Allergy.*2015;2(4):294-306.

4. Giavina-Bianchi P, Aun MV, Motta AA, Kalil J, Castells M. Classification of angioedema by endotypes. *Clin Exp Allergy.*2015;45(6):1142-1143.

5. Azofra J, Díaz C, Antépara I, Jaúregui I, Soriano A, Ferrer M. Positive response to omalizumab in patients with acquired idiopathic nonhistaminergic angioedema. *Ann Allergy Asthma Immunol.*2015;114(5):418-419.

6. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy Eur J Allergy Clin Immunol.*2018;73(7):1393-1414.

7. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report1.*Allergy Eur J Allergy Clin Immunol.* 2011;66(3):317-330.

8. Sabaté-Brescó M, Rodriguez-Garijo N, Azofra J, et al. A Comparative Study of Sex Distribution, Autoimmunity, Blood, and Inflammatory Parameters in Chronic Spontaneous Urticaria with Angioedema and Chronic Histaminergic Angioedema. *J Allergy Clin Immunol Pract.*2021;9(6):2284-2292.

9. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy Eur J Allergy Clin Immunol.*2017;72(12):2005-2016.

10. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire.*Allergy Eur J Allergy Clin Immunol.* 2012;67(10):1289-1298.

11. Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Björkander J. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy Asthma Proc.*2017;38(6):447-455.

12. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Ann Allergy Asthma Immunol.* 2020;124(6):600-607.

13. Caballero T, Prior N. Burden of illness and quality-of-life measures in angioedema conditions. *Immunol Allergy Clin N Am.*2017;37(3):597-616.

14. Folci M, Heffler E, Canonica GW, Furlan R, Brunetta E. Cutting edge: biomarkers for chronic spontaneous urticaria. *J Immunol Res.*2018;2018:1-12.

15. Kolkhir P, André F, Church MK, Maurer M, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. *Clin Exp Allergy.*2016;47(1):19-36.

16. Puxeddu I, Petrelli F, Angelotti F, Croia C, Migliorini P. Biomarkers in chronic spontaneous urticaria: current targets and clinical implications. *J Asthma Allergy.* 2019;12:285-295.

17. Weller K, Groffik A, Magerl M, et al. Development, validation, and initial results of the angioedema activity score. *Allergy Eur J Allergy Clin Immunol.* 2013;68(9):1185-1192.

18. Stull D, McBride D, Tian H, et al. Analysis of disease activity categories in chronic spontaneous/idiopathic urticaria. *Br J Dermatol.* 2017;177(4):1093-1101.

19. Sussman G, Abuzakouk M, Bérard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. *Allergy Eur J Allergy Clin Immunol.*2018;73(8):1724-1734.

20. Balañá M, Valero A, Arnau AG, Ferrer M, Jauregui I, Ballesteros C. Validation of the Spanish version of the urticaria activity score (Uas) and its use over one week (Uas7). *Value Health.* 2015;18(7):A426.

21. Maurer M, Giménez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med.*2019;381(14):1321-1332.

22. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med.*2013;368(10):924-935.

23. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. *Br J Dermatol.*1999;140(4):667-671.

24. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol.*2006;154(2):294-298.

25. Ue AP, Souza PK, Rotta O, Wde JF, Lima AR, Sabbag DS. Quality of life assessment in patients with chronic urticaria. *An Bras Dermatol.* 2011;86(5):879-904.

26. Cavariani Silvares MR, Parise Fortes MR, Miot HA. Qualidade de vida em urticária crônica: inquérito em ambulatório público universitário, Botucatu (Brasil). *Rev Assoc Med Bras.* 2011;57(5):577-582.

27. Choi WS, Lim ES, Ban GY, et al. Disease-specific impairment of the quality of life in adult patients with chronic spontaneous urticaria.*Korean J Intern Med.* 2018;33(1):185-192.

28. Maurer M, Sofen H, Ortiz B, Kianifard F, Gabriel S, Bernstein JA. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: analyses according to the presence or absence of angioedema. *J Eur Acad Dermatology Venereol.* 2017;31(6):1056-1063.

29. Oles-Krykowska A, Badura-Brzoza K, Brzoza Z. Does angioedema influence the quality of life in patients with chronic spontaneous urticaria? *Ann Allergy Asthma Immunol.* 2019;122(5):539-541.

30. Kolkhir P, Altrichter S, Hawro T, Maurer M. C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. *Allergy Eur J Allergy Clin Immunol.* 2018;73(4):940-948.

31. Takeda T, Sakurai Y, Takahagi S, et al. Increase of coagulation potential in chronic spontaneous urticaria. *Allergy Eur J Allergy Clin Immunol.* 2011;66(3):428-433.

32. Schmetzer O, Lakin E, Topal FA, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2018;142(3):876-882.

33. Grattan CEH, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin Exp Allergy.* 2003;33(3):337-341.

34. Kolkhir P, Church MK, Altrichter S, et al. Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. *J Allergy Clin Immunol Pract.* 2020;8(1):318-325.

35. Jauregui I, Gimenez-Arnau A, Bartra J, et al. Psychometric properties of the Spanish version of the once-daily Urticaria Activity Score (UAS) in patients with chronic spontaneous urticaria managed in clinical practice (the EVALUAS study). *Health Qual Life Outcomes.*2019;17(1):1-9.

Tables

Table 1. Demographic, episode, treatment and emergency features of the patients.

	CHA (n=68)	**CSU-AE (n=63)**	**p-va**
Gender, male [n (%)]	30 (44.1%)	17 (27.0%)	**0.04**
Male/female ratio	0.78	0.36	
Age, years [mean (range)]	53.1 (20–85)	47.4 (20–76)	**0.03**
AE episode, duration [n (%)]			0.181
1–3 hours	2 (2.9%)	3 (4.8%)	
3–6 hours	9 (13.2%)	6 (9.5%)	
6–12 hours	14 (20.6%)	15 (23.8%)	
12–24 hours	9 (13.2%)	13 (20.6%)	
24–28 hours	12 (17.7%)	17 (27.0%)	

	CHA (n=68)	**CSU-AE (n=63)**	**p-va**
2–3 days	15 (22.1%)	8 (12.7%)	
3–6 days	7 (10.3%)	1 (1.6%)	
AE episodes past 12 months [median (iqr)]	6 (3–14)	4.5 (2–12)	0.390
Treatment [n (%)]	47 (69.12%)	52 (82.54%)	0.096
H1-antihistamine [n (%)]	36 (52.94%)	50 (79.37%)	**0.00**
single dose [n (%)]	24 (35.29%)	27 (42.86%)	0.375
updose [n (%)]	12 (17.65%)	23 (36.51%)	**0.01**
double dose [n (%)]	10 (14.71%)	13 (20.63%)	0.373
triple dose [n (%)]	1 (1.47%)	4 (6.35%)	0.145
quadruple dose [n (%)]	1 (1.47%)	6 (9.52%)	**0.04**
Corticosteroid [n (%)]	9 (13.24%)	13 (20.63%)	0.694
Omalizumab [n (%)]	3 (4.41%)	0	0.086
Others [n (%)]	4 (5.88%)	9 (14.29%)	0.285
Number of treatments [median (iqr)]	1 (1–1)	1 (1–2)	**0.04**
Patient visits to an emergency department since diagnosis [n (%)]	41 (60.3%)	45 (71.4%)	0.180
Number of visits to an emergency department [n (%)]$^{+}$			0.333
0 visits	0	2 (4.2%)	
1 visits	9 (22.5%)	7 (14.6%)	
2 visits	10 (25%)	7 (14.6%)	
3 visits	2 (5%)	7 (14.6%)	
4 visits	7 (17.5%)	5 (10.4%)	
5 visits	4 (10%)	6 (12.5%)	
>5 visits	8 (20%)	14 (29.2%)	
Number of visits to an emergency department past 12 months [median (iqr)]	1 (0–2)	2 (1–4)	**0.01**

$^{+}$Results from 43 patients were not obtained (28 in the IH-AAE group and 15 in the CSU-AE group).

Statistically significant differences are highlighted in bold.

Table 2. Disease activity and quality of life of the patients.

	CHA (n=68)	**CSU-AE (n=63)**	**p value**
AAS7 [median (iqr)]	0 (0–1)	1 (0–1)	**0.022**
AAS7 levels [n (%)]$^{+}$			0.089
No	36 (58.1%)	22 (42.3%)	0.094
Low	20 (32.3%)	20 (38.5%)	0.489
Moderate	6 (9.7%)	6 (11.5%)	0.747
High	0	4 (7.7%)	**0.041**
AE-QoL [median (iqr)]$^{++}$	18 (4–40)	37 (10–65)	**0,005**
Functioning	0 (0–19)	25 (0–56)	**< 0.001**
Fatigue/Mood	15 (0–40)	35 (0–65)	**0.012**
Fear/Shame	38 (0–58)	50 (21–79)	**0.031**
Nutrition	0 (0–13)	25 (0–50)	**0.007**
UAS7 [median (iqr)]		3.75 (0–17)	
UAS 7 levels [n (%)] §			
No		15 (33.3%)	
Low		14 (31.1%)	
Moderate		13 (28.9%)	
High		3 (6.7%)	

	CHA (n=68)	CSU-AE (n=63)	p value
CU-QO2 L [median (iqr)]		49 (27–66)	

[+]Results from 17 patients were not obtained (6 in the CHA group and 11 in the CSU-AE group).

[++]Results from 5 patients were not obtained (1 in the IH-AEE group and 4 in the CSU-AE group).

[§]Results from 18 patients were not obtained.

AAS7 level was categorized as follows: no episodes (0), low (1–6), moderate (7–18), high (19–105).

UAS7 levels were categorized as follows: no episodes (0), low (1–6), moderate (7–27), high (28–42).

Statistically significant differences are highlighted in bold.

Figure legends

Figure 1. Angioedema Quality of Life questionnaire by the severity of the attacks on the Angioedema Activity Score. A) Total AE-QoL score in CHA and CSU-AE grouped according to the AAS7 score levels as follows: no episodes (AAS7:0), low (1–6), moderate (7–18) and high (19–105). B) AE-QoL score of the different dimensions in CHA and CSU-AE with patients grouped according to the AAS7 score levels.

Figure 2. Levels of the different biomarkers (PCR, D-dimer, basophil counts, eosinophil counts, and total IgE) in patients categorized according to UAS7 in CSU-AE (A) and AAS7 in CSU-AE (B) and CHA (C). Individual data are presented, with values shown as the mean and SD.