Predictive model to differentiate chronic histaminergic angioedema and chronic spontaneous urticaria with angioedema

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Background: Chronic histaminergic angioedema (CHA) may be classified as a separate acquired angioedema (AE) or as an endotype of chronic spontaneous urticaria (CSU). A recent study suggested them to be independent pathologies.
Objective: We carried out an exhaustive analysis between CHA and AE-CSU to explore the possible differentiation between them on the bases of a series of predictors.
Methods: An observational, retrospective, cross-sectional, and exploratory study was designed. Fifty-six CHA and 40 AE-CSU patients were included. Data were extracted from the year before and year after time of diagnosis. A predictive model was generated by logistic regression, and its discriminatory power was assessed using the area under the receiver operating characteristic curve.
Results: The average frequency of AE attacks per year turned out to be higher in the AE-CSU group than in the CHA group, both before (median [interquartile range] 12 [43] vs 8 [16]) and after (24.3 [51.2] vs 2 [4.25]) diagnosis, respectively. The uvula was more frequently affected in CHA. No other differences were found. However, using 7 clinical characteristics of the patients, a multiple logistic regression model was able to predict, with a specificity of 86.4%, a sensitivity of 92.3%, and an area under the curve of 95.1% ($P = .024$), that CHA and AE-CSU behaved differently.
Conclusion: CHA has similar characteristics to AE-CSU, although they slightly differed in the frequency of attacks and their location. Despite its similarities, a multiple logistic regression model that used clinical and evolutionary characteristics allowed the differentiation of both pathologies and supports the idea that these 2 entities are independent. (J Allergy Clin Immunol Global 2024;3:100278.)

Key words: *Angioedema, chronic spontaneous urticaria, histaminergic angioedema, multiple logistic regression model*

Abbreviations used
AAS: Angioedema Activity Score
AE: Angioedema
AE-BK: Bradykinin-mediated AE
AE-MC: Mast cell–mediated AE
AE-QoL: Angioedema Quality of Life Questionnaire
CHA: Chronic histaminergic AE
CRP: C-reactive protein
CSU: Chronic spontaneous urticaria
ESR: Erythrocyte sedimentation rate
LTP: Long-term prophylaxis
QoL: Quality of life
ROC: Receiver operating characteristic
TSH: Thyroid-stimulating hormone

Progress in the knowledge and treatment of angioedema (AE) has been notable in recent decades. However, chronic histaminergic AE (CHA) continues to be a challenge in daily clinical practice because of its similarity to other forms of AE and because of the absence of biomarkers, making its diagnosis more complex.

CHA is defined as the presence of episodes of recurrent AE that are responsive to treatment with antihistamines, corticosteroids, adrenaline, and/or omalizumab, without an identifiable cause.[1] This definition is identical to the definition of AE present in chronic spontaneous urticaria (CSU). According to "The International EAACI/GA^{2}LEN/EuroGuiDerm/APAACI Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria," published in 2022, isolated idiopathic AE is considered a subtype of CSU.[2] It is currently debated whether these cases of recurrent AE as the only symptom correspond to different CSU phenotypes or to independent entities.[3]

The differentiation of CHA from other forms of AE is based on the response of the AE episodes to antihistamines, corticosteroids, adrenaline, or omalizumab and on the absence of an identifiable allergic cause.[1] In this sense, CHA is apparently easily distinguishable from bradykinin-mediated AE (AE-BK), first because of its lack of response to these medications[4] and second as a result of the presence of altered complement levels, as is the case of hereditary AE due to C1 inhibitor deficiency (aka HAE-C1INH). However, the differentiation of CHA from other forms of mast cell–mediated AE (AE-MC) is more complex. When a patient with CSU manifests AE without hives, the single AE episode may appear indistinguishable from CHA.

Studies comparing CHA with other AE are scarce.[5,6] The only study contrasting AE-CSU and CHA is by Sabaté-Brescó et al.[7] They suggest that there are several characteristics that can differentiate both entities and propose to classify them independently.

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We have carried out an exhaustive analysis by constructing a statistical model to check whether it is possible to accurately differentiate between these entities.[7,8]

In the allergology field, published articles that use these models are few; sometimes their use is reduced because of the sheer complexity of the mathematical modeling. Some of the articles we found use these models to predict the risk of allergic reaction to a drug,[9] analyze the variables that were best related to good adherence to omalizumab in severe asthma,[10] or investigate, in patients with allergic contact dermatitis, which clinical factors are most relevant to establish earlier patch testing.[11] However, none has been developed in the field of AE to date.

The aim of this study was to carry out a comparative study between CHA and AE-CSU and obtain a predictive model to explore the possible differentiation between CHA and AE-CSU on the bases of a series of predictors.

METHODS

Design

An observational, retrospective, cross-sectional, and exploratory study was designed in which 56 patients with CHA and 40 with AE-CSU were included between 2017 and 2021; they were recruited from the AE consultation of the allergy service at the Gregorio Marañón General University Hospital. The study was approved by the ethics committee and was divided into 2 parts. The first involved data collection, mainly the clinical history; the second was a telephone interview in respondents answered a quality of life (QoL) survey: the Angioedema Quality of Life Questionnaire (AE-QoL).[12] All patients were older than 18 and gave informed consent to participate in the study.

The inclusion criteria for CHA required the presence of recurrent AE that responded to antihistamines, corticosteroids, adrenaline, or omalizumab. The exclusion criteria were patients with AE of allergic etiology, any patient with CSU, patients with urticaria/AE due to delayed pressure or vibratory AE, and patients with urticaria/AE induced by (and not exacerbated by) nonsteroidal anti-inflammatory drugs. The inclusion criteria for AE-CSU required the presence of recurrent AE associated with CSU that responded to treatment with antihistamines, corticosteroids, adrenaline, or omalizumab. All patients had normal C3, C4, C1INH, and C1q protein levels as well as normal C1INH activity.

Variables collected were date of birth, sex, personal history of allergy and autoimmune diseases, cardiovascular risk factors, family history of AE, age at first episode of AE, and age at diagnosis. The number and location of attacks as well as the duration of AE attacks during the year before and the year after diagnosis were analyzed. The total number of patients for each location was counted and results expressed as percentages. In addition, the presence of triggers and prodromes, treatment of acute attacks, long-term prophylaxis (LTP) treatment, visits to the emergency department, and cycles of corticosteroid therapy administered were recorded. The following laboratory data were analyzed at the time of diagnosis: basophil numbers, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, thyroid-stimulating hormone (TSH), thyroid antibodies, and total IgE levels. Also, once diagnosed and receiving basic treatment, 49 CHA and 38 AE-CSU patients completed the AE-QoL.

Statistical analysis

Statistical analysis was carried out by the freely distributed software Jamovi 2.0 (2021) and Microsoft Excel 2013 (Microsoft, Redmond, Wash).

Depending on the distribution of the data, qualitative variables were expressed as relative and absolute frequencies, whereas quantitative variables were expressed as means and standard deviations or medians and interquartile ranges.

For the comparison between groups in categorical variables, a chi-square test was used; for quantitative variables, ANOVA was used for data with a normal distribution, and its nonparametric variant, Kruskal-Wallis, was used when data did not meet the assumption of normality. The results were considered statistically significant when $P < .05$ was obtained.

To further differentiate the CHA from the AE-CSU, a logistic regression analysis was carried out, in which both variables acted as a dichotomous dependent variable to be predicted. To evaluate the influence of each of the predictors, the odds ratio was used.

To create the model, all the predictor variables were introduced, and the variance inflation factor was calculated for each of them to eliminate collinearity. Those predictors that presented strong correlations with the rest (with a variance inflation factor value of >5) were expelled to develop the final model reliably. Using the Hosmer-Lemeshow test, it was tested whether the proposed model fit correctly given the data collected, and the model was validated through 5-fold cross-validation. Finally, for the resulting predictive model, the parameters of sensitivity, specificity, and predictive values were estimated using 95% confidence intervals, and its discriminant capacity was evaluated using the area under the receiver operating characteristic (ROC) curve estimated by a 95% confidence interval. The results were considered statistically significant when $P < .05$ was obtained.

RESULTS

Sociodemographic characteristics, comorbidities, and family history

No significant differences in sex distribution or mean age were found between groups. The mean age at symptoms onset and confirmed diagnosis, as well as the years of diagnostic delay, were similar in both types of AE. No differences were found in terms of family history (Table I).

In contrast, the CHA group presented statistically significantly more cardiovascular risk factors than the AE-CSU group, especially dyslipidemia. Both groups had similar backgrounds of atopy or autoimmune diseases.

Characteristics of AE

The average frequency of AE attacks per year was significantly higher in the AE-CSU group than in the CHA group, both the year before (median AE-CSU of 12 vs 8 of CHA, $P = .002$) and the year after diagnosis (median AE-CSU of 24 vs 2 of CHA, $P = .003$). No differences were found in terms of duration of symptoms (Table II).

AE episodes at the oropharynx were significantly more frequent in the CHA group than in the AE-CSU group (46% of CHA vs 17% of AE-CSU, $P = .024$), especially uvular AE (12% of CHA vs 0 of AE-CSU, $P = .02$). A trend was observed among patients with CHA to present a higher proportion of tongue AE, but no statistical differences were reached. No patient required

TABLE I. Sociodemographic characteristics and comorbidities

Characteristic	CHA	AE-CSU	*P* value
Sex (male), no. (%)	18 (32)	17 (42.5)	.299
Male/female ratio	0.47	0.73	
Age (years), mean (SD)	54.1 (17.5)	50.4 (18.2)	.316
Age at symptom onset (years), mean (SD)	44.4 (17.1)	42.2 (17.3)	.542
Age at diagnosis (years), mean (SD)	48 (16)	44.8 (17.5)	.375
Diagnosis delay (years), mean (SD)	3.58 (5.86)	2.64 (4.63)	.384
Atopy (yes), no. (%)	20 (35.7)	21 (52.5)	.101
Cardiovascular risk factors, no. (%)	17 (30.3)	4 (10)	.017
High blood pressure, no. (%)	11 (64.7)	4 (10)	.2
Diabetes, no. (%)	5 (29.4)	0	.052
Dyslipidemia, no. (%)	11 (64.7)	0	.005
Autoimmune disease (yes), no. (%)	15 (26.7)	9 (22.5)	.633
AE family history (yes), no. (%)	3 (5.35)	2 (5)	.938

SD, Standard deviation.

TABLE II. Clinical features of AE

Characteristic	CHA	AE-CSU	*P* value
AE episode, annual frequency before diagnosis			
Mean (SD)	15 (17.8)	46.8 (70.9)	.002
Median (IQR)	8 (16)	12 (43)	
AE episode, annual frequency after diagnosis			
Mean (SD)	3.41 (4.5)	5.5 (22)	.003
Median (IQR)	2 (4.25)	24.3 (51.2)	
AE episode, duration (hours) before diagnosis			
Mean (SD)	31 (24.7)	22.9 (17.3)	.078
Median (IQR)	24 (36)	24 (12.5)	
AE episode, duration (hours) after diagnosis			
Mean (SD)	9.8 (17.8)	12.7 (13.6)	.398
Median (IQR)	2 (12)	6 (22)	
Affected areas			
Facial	51 (91.07)	38 (95)	.841
Maxillary region	26 (46.42)	11 (27.5)	.06
Eyelid	22 (39.28)	16 (40)	.944
Lips	38 (67.85)	28 (70)	.823
Oropharynx	26 (46.42)	7 (17.5)	.024
Tongue	19 (33.9)	7 (17.5)	.074
Uvula	7 (12.5)	0	.02
Pharyngolarynx	5 (8.92)	3 (7.5)	.803
Peripheral attacks	17 (30.3)	20 (50)	.051
Trunk	0	0	—
Extremities	17 (30.3)	20 (50)	.051
Abdomen	0	0	—
Genitalia	3 (5.35)	3 (7.5)	.669
Trigger (yes)	20 (35.7)	17 (42.5)	.359
Stress	8 (14.2)	6 (15)	.841
NSAID	8 (14.2)	6 (15)	.841
Mechanical pressure	4 (7.1)	5 (12.5)	.294
ACEI	1 (1.7)	0	.583
Physical trauma	1 (1.7)	0	.583
Prodrome (yes)	12 (26.7)	10 (25)	.844
Pruritus	9 (16)	9 (22.5)	.296
Paresthesia	5 (9)	1 (2.5)	.199
Fatigue/discomfort	1 (1.7)	0	.583

Data are presented as nos. (%) unless otherwise indicated.
ACEI, Angiotensin-converting enzyme inhibitor therapy; *IQR,* interquartile range; *NSAID,* nonsteroidal anti-inflammatory drug; *SD,* standard deviation.

intubation or tracheostomy in the study. Gastrointestinal AE was not observed in any group. No significant differences were found in other locations or regarding the presence of triggers or prodromes preceding the attacks.

No significant differences were found in any blood count or serologic markers such as basophil numbers and ESR, CRP, D-dimer, TSH, thyroid antibody, and total IgE levels (Table III).

TABLE III. Hematologic results

Characteristic	CHA (n = 56)	AE-CSU (n = 23)	*P* value
Basophil numbers (/mm^3)	54.3 (141)	17.4 (38.8)	.221
CRP (mg/L)	0.64 (0.75)	2.32 (5.73)	.322
ESR (mm/h)	8.79 (7.53)	11 (8.98)	.367
d-Dimer (ng/mL)	140 (196)	228 (136)	.278
TSH (μU/mL)	2.32 (1.08)	2.01 (1.07)	.308
Patients with thyroid antibodies, no. (%)	5 (8.9)	4 (7.14%)	.280
IgE level (kU/L)	151 (180)	161 (204)	.848

Data are presented as means (standard deviations) unless otherwise indicated.

TABLE IV. Treatment before and after diagnosis

	Before diagnosis			After diagnosis		
Characteristic	CHA	AE-CSU	*P* value	CHA	AE-CSU	*P* value
Acute attack treatment						
Treatment	51 (91.1)	39 (97.5)	.199	39 (69.7)	32 (80)	.365
Second-generation H_1 antihistamines	44 (78.5)	31 (77.5)	.546	33 (58.4)	30 (75)	.156
Single dose	12 (21.4)	31 (77.5)	<.0001	30 (53.5)	29 (72.5)	.095
Double dose	32 (57.1)	0	<.0001	3 (5.35)	1 (2.5)	.444
Corticosteroid	38 (67.8)	25 (62.5)	.740	12 (21.4)	13 (32.5)	.324
Adrenalin	5 (8.9)	0	.062	0	0	—
Montelukast	5 (8.9)	0.062	6 (10.7)	1 (2.5)	.128	
LTP						
Treatment	33 (58.9)	28 (70)	.371	31 (55.6)	32 (80)	.022
Second-generation H_1 antihistamines	33 (58.8)	24 (60)	.920	31 (55.6)	32 (80)	.022
Single dose	20 (35.7)	15 (37.5)	.862	21 (37.8)	17 (42.5)	.777
Double dose	12 (21.4)	8 (20)	.920	6 (10.7)	12 (30)	.033
Quadruple dose	1 (1.7)	1 (2.5)	.662	4 (7.1)	3 (7.5)	.621
Montelukast	1 (1.7)	4 (10)	.094	2 (3.5)	5 (12.5)	.104
Tranexamic acid	1 (1.7)	0	.583	1 (1.7)	0	.583
Patients visiting emergency department						
No. of visits per year	73	82	.201	4	22	.921
No. of corticosteroid prescriptions per year	47	84	.552	3	43	.042

Data are presented as nos. (%) unless otherwise indicated.

Treatment and emergency features

Both groups were treated with the same medication. However, the need for treatment and its dose was different between groups. The proportion of patients who required higher doses (double-dose) of second-generation H_1 antihistamines for acute attacks before diagnosis was significantly higher in CHA patients. After diagnosis, no differences were found.

Regarding LTP, once the disease was diagnosed, the proportion of patients who were prescribed LTP was significantly higher in AE-CSU patients (80%) than CHA patients (55.6%), and the need for double-dose H_1 antihistamines was significantly higher in the AE-CSU group. Also, the number of corticosteroid cycles administered during the year after diagnosis was significantly higher in the AE-CSU group. The number of visits to the emergency department were similar between groups (Table IV).

QoL studies

The AE-QoL questionnaire was given to 49 patients with CHA and 38 patients with AE-CSU to evaluate the QoL impairment based on the AE episodes that occurred in the 4 previous weeks. Patients with CHA tend to present a slightly better QoL than patients with AE-CSU. However, the differences were not significant (Table V).

Predictive model to evaluate whether CHA and AE-CSU correspond to different entities

We have already demonstrated the presence of slight differences in location of attacks, frequency of episodes, and need for treatment. However, no differences were found in the rest of the analyzed features. To investigate if the differences found were sufficient to support the hypothesis that whether CHA and AE-CSU corresponded to different entities, a multiple logistic regression model was carried out to evaluate this theory from another perspective.

To this end, the type of AE (CHA or AE-CSU) was selected as dependent variable and the following as independent variables: sex, age at symptom onset, duration of AE episodes in the year before and after diagnosis, mean annual frequency of AE attacks before and after diagnosis, blood markers (CRP, D-dimer, ESR, IgE, TSH, presence of anti-thyroid antibodies, and basophil numbers), total AE-QoL score and its dimensions score, and location of AE episodes.

After the variable selection process, the final variables that remained in the model were as follows: duration of AE episode before diagnosis, mean annual frequency of AE before diagnosis, ESR, presence of thyroid antibodies and basophil numbers, AE-QoL total score, and the following locations of AE episodes: tongue, lips, uvula, pharyngolarynx, maxillary region, eyelid,

TABLE V. AE-QoL results

Characteristic	CHA (%) (n = 49)	AE-CSU (%) (n = 38)	*P* value
AE-QoL total score	16.4 (15.79)	29.44 (15.09)	.4237
Functioning	5.86 (13.64)	11.18 (26.56)	.229
Fatigue mood	15.51 (20.97)	16.44 (25.46)	.851
Fear/shame	26.87 (23.90)	33.77 (26.7)	.208
Food	8.67 (20.76)	15.13 (43.75)	.225

Data are presented as means (standard deviations).

TABLE VI. Multiple logistic regression analysis

Independent variable	Estimate	*P* value	OR	95% CI
Constant	−0.6163	.778	0.540	0.00742-39.27
Duration of AE episode before diagnosis (hours)	−0.1112	.570	1.072	0.842-1.37
Annual frequency of AE before diagnosis	0.0152	.584	0.982	0.920-1.05
ESR	−0.0953	.284	0.902	0.747-1.09
Thyroid antibodies	2.0395	.570	0.673	0.172-2.63
Basophil numbers	−0.0147	.447	1.026	0.960-1.10
AE-QoL score	0.0794	.523	0.971	0.887-1.06
Tongue	−1.1112	.997	1.008	0.024-41.42
Lips	2.0883	.093	0.019	2.00^{e-4}-1.93
Uvula	−39.2524	.996	9.74^{e+7}	0.000-Inf
Pharyngolarynx	19.2464	.718	0.234	8.99^{e-5}-614.02
Maxillary region	−1.9050	.251	7.362	0.242-223.28
Eyelid	0.3442	.874	0.750	0.021-26.38
Extremities	1.4569	.909	1.194	0.057-24.87
Genitalia	20.6453	1.000	18.201	0.000-Inf

Estimate refers to estimates of regression coefficients; *OR* (odds ratio), probability of occurrence of event divided by probability otherwise; and *CI,* confidence interval.

extremities, and genitalia. We describe below the model resulting from introducing all these variables (Table VI). No separate variable reached statistical significance on its own. However, when performing the Hosmer-Lemeshow test to check whether the proposed model overlapped with reality, it was observed that the entire model did present statistical significance ($\chi^2 = 26.3$; $df = 14$; $P = .024$).

To verify the prediction of the model, a ROC curve was constructed, which showed that, with a specificity of 86.4%, a sensitivity of 92.3%, and an area under the curve of 95.1% ($P = .024$), when 2 patients with CHA and AE-CSU present simultaneously, the model was able to predict which patient had which diagnosis 95.1% of the time (Fig 1), by means of the following equation:

$$\ln[E(Y_i|X_i = x_i)] = \beta_0 + \beta_1 x_i + \cdots + \beta_i x_i$$

Here, β_0 is the intercept or constant in this model (its value is −0.6163), and β_1-β_i is the estimate value for each independent variable (x_i) (Table VI). In this way, Eqn 1 allows us to differentiate during clinical practice, with a probability from 0 to 1, whether the diagnosis is CHA (probability close to 1) or AE-CSU (probability close to 0). We can therefore infer that they are different and distinguishable entities because the model is capable of differentiating between them according to the values of their predictors.

DISCUSSION

When a patient with CSU presents an episode of AE without wheals, it may clinically appear indistinguishable from CHA. As a consequence, recurrent histaminergic AE can be classified as an endotype of CSU.[2] However, CHA may have differential characteristics and could also be considered an independent type of AE.[1] Differentiating CHA from other forms of AE consists of clinical diagnosis, which is in turn based on the response of AE episodes to antihistamines, corticosteroids, adrenaline, or omalizumab as well as on the absence of an identifiable allergic cause that justifies the appearance of the AE.[1] In this way, CHA is apparently easily distinguishable from AE-BK.[13] However, differentiating CHA from other forms of AE-MC may prove more complex.

Since the HAWK described the new classification of AE, in 2014,[1] there have been occasional comparative studies that have delved deeper into the differences between the various forms of AE. Maurer and Magerl[4] in 2021 published a review that, based on the literature, explained the clinical and sociodemographic features that differentiate different forms of AE-BK and AE-MC. Can et al[14] and Ohsawa et al[15] published studies comparing clinical and QoL characteristics of AE-BK and AE-MC; however, all included isolated AE without hives and AE associated with CSU as a single entity.

In 2021, Sabaté-Brescó et al[7] showed that there are several features such as differences in sex, age, affected areas, basopenia, and antibodies against IgE, which would allow them to be considered independent entities.

In this work, an exhaustive, comparative analysis was executed between both entities to explore whether these correspond to 1 or 2 independent diseases.

The first difference found in our study between CHA and AE-CSU is the annual frequency of AE episodes, which seems higher in the AE-CSU group. In this work, disease activity was measured by number of attacks, not by the Angioedema Activity Score (AAS) questionnaire.

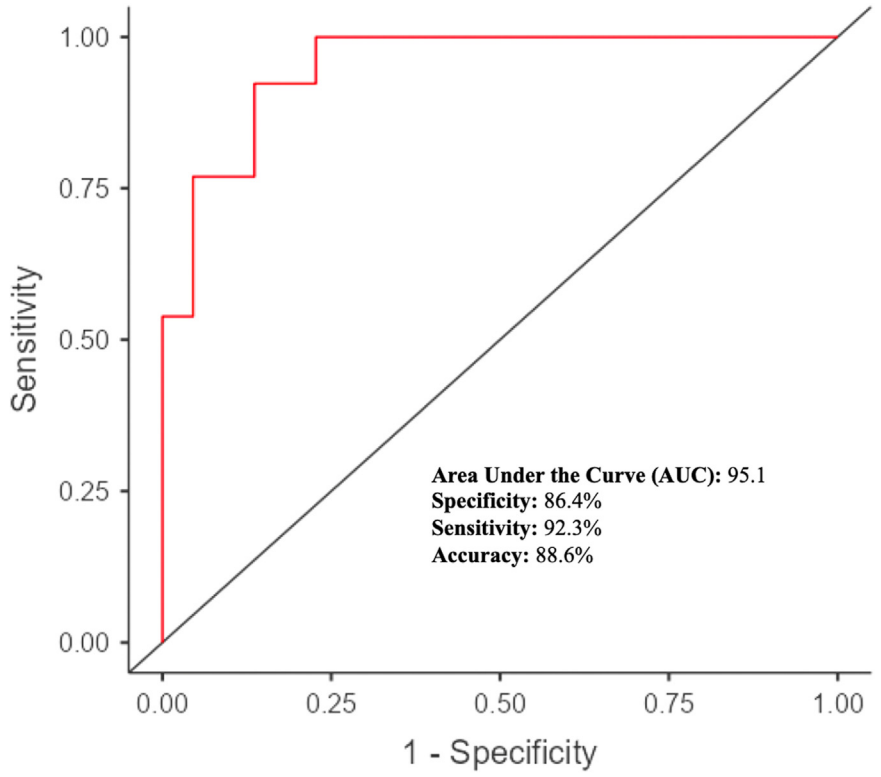

FIG 1. ROC curve multiple logistic regression model. Curve evaluates discriminative capacity of diagnostic test with 2 categories. Graph represents sensitivity (probability of detecting truly positive result) against false-positive rate (probability complementary to specificity, represented on x-axis as 1 − Specificity). Area under ROC curve is interpreted as probability of successfully distinguishing CHA and AE-CSU when presenting simultaneously. Our model does this correctly 95.1% of the time.

Rodríguez-Garijo et al[8] did not report any difference in terms of frequency of episodes in the last 12 months between both entities. However, when calculating the disease activity using the AAS7, it was higher in the AE-CSU group (median 1) than in the CHA group (median 0, $P = .022$). Furthermore, when dividing patients into different groups according to AAS7 level of activity, no patient with CHA presented a severe AAS level.

The mean duration of AE attacks was not significantly different, although there was a trend toward a longer duration of AE episodes before diagnosis in the CHA group, as observed by Sabaté-Brescó et al.[7] In that study, it was shown that duration of episodes of more than 48 hours were significantly more frequent in the CHA group.[8]

Second, CHA and AE-CSU differ in their oropharyngeal location, representing the most remarkable difference between both entities. Oropharyngeal attacks were more frequent in the CHA group (46% of CHA vs 17% of AE-CSU, $P = .024$), especially uvular AE (12% of CHA vs 0 of AE-CSU, $P = .02$). Furthermore, a trend among patients with CHA to present a higher proportion of lingual AE was found. Sabaté-Brescó et al,[7] in contrast, found labial and eyelid AE to be more prominent in the AE-CSU group, and tongue AE to be significantly more frequent in CHA patients (58.8%, vs 29.03% in AE-CSU, $P = .008$%). Instead, uvular AE was equally frequent in both groups. No patient their study or ours required intubation or tracheostomy.

The proportion of patients who required a double dose of second-generation antihistamines to treat acute attacks was significantly higher in the CHA group (57, 1%, vs 0 in AE-CSU, $P < .0001$). However, once the disease was diagnosed, a greater proportion of patients with AE-CSU (80%) required LTP than patients with CHA (55.6%, $P = .022$), and the need for double-dose antihistamine was higher (30% vs 10.7%, $P = .033$). It seems that in CHA, episodes are less frequent but more intense, and that is why patients need less LTP.

Rodríguez-Garijo et al[8] found that the proportion of patients who required LTP was also higher in the AE-CSU group (79.37%, vs 52.94% in CHA; $P = .001$), and the need for updosing second-generation H_1 antihistamines was also significantly higher in AE-CSU patients. A similar result was provided by van den Elzen et al,[16] who compared the response to second-generation H_1 antihistamines in patients with isolated AE, AE-CSU, and CSU, observing that the use of supratherapeutic doses as LTP was significantly higher in the groups with hives than in those with isolated AE. Yet the number of annual corticosteroid prescriptions was higher in the AE-CSU group. In this case, most of the time, corticosteroids are prescribed because of the presence of AE rather than the presence of hives.

Also, Rodríguez-Garijo et al[8] found that the median number of visits to the emergency department in the last 12 months was higher in patients with AE-CSU (average of 2) than in patients with CHA (average of 1, $P = .015$).

The different ways of responding to medication would be another differential feature, although this comparison is difficult because, in the case of AE-CSU, not only AE is being treated but

also the presence of hives and pruritus, which may sometimes be intense.

Regarding the rest of the variables compared in the study, no other individual differences were found. We found no significant differences in terms of sex; Sabaté-Brescó et al,[7] in contrast, found significant differences in the proportion of women in the AE-CSU group (0.36), which turned out to be significantly higher than in the CHA group (0.78, $P = .0466$).

In our study, no significant differences were found in any blood count or serologic markers such as basophil numbers, ESR, CRP, TSH, antithyroid antibodies, and total IgE levels extracted from the first analysis performed during consultation. Sabaté-Brescó et al[7] found that the total numbers of basophils were significantly lower in the AE-CSU group (420 vs 690 in CHA, $P < .0001$), especially in patients with associated autoimmune diseases. Furthermore, it was shown that 31.5% of sera from patients with AE-CSU were able to activate healthy basophils, which was not seen in patients with CHA. IgG anti-FcεRI was reported in 35% to 60% of adult patients with CSU.[17-20] Unfortunately, no such studies were done in our patients. One of the limitations of our work is not having complementary experimental diagnostic tools.

CHA has similar characteristics to AE-CSU, although in general, episodes of AE are less frequent throughout the year; they also differ in some of their oropharyngeal locations, and the need for LTP is less common than in patients with AE-CSU. In view of this, because the differences between both entities were small and not always superimposable with other studies, it was decided to develop a tool to evaluate, from another perspective, whether the differences found in this study had sufficient weight to consider CHA and AE-CSU as different entities. A mathematical model—specifically, a logistic regression model—was built to objectively resolve this hypothesis. Given the values of the independent variables, a prognostic index (an equation) was constructed to predict a certain condition—in this case, having CHA or AE-CSU.

The predictive mathematical model, developed through multiple logistic regression analysis, calculated the probability a patient has of developing CHA or AE-CSU according to a series of independent variables (ie, those, all related to the AE, analyzed in our study). It was observed that, given 2 patients, 1 each with CHA and AE-CSU, our model was able to predict, using an equation, whether the diagnosis was CHA or AE-CSU with a specificity of 86.4% and a sensitivity of 92.3%. Furthermore, the model was validated using the *K*-fold cross-validation method. In this way, we support the hypothesis raised by Sabaté-Brescó et al[7] that, despite their similarities, they are actually different entities, since the model is capable of differentiating between them, thanks to the joint assessment of 7 clinical and evolutionary variables.

According to our results, with high sensitivity and specificity, the entire model acquired statistical significance even though no variable on its own did. This last point is important. Because we are looking for the best-performing model, we present a multivariate model in which no variable by itself is significant, but it is significant when they act together. All these variables are necessary to make the distinction between CHA and AE-CSU.

It is curious that the variables that our model chose as definitive for the construction of the equation (duration and frequency of episodes before diagnosis, location of episodes, total score of AE-QoL, absolute level of basophils, and levels of ESR and antithyroid antibodies) were a large part of them yet the ones our study presented as features that would permit both forms of AE to be differentiated. The only variables that our model adopted as necessary but that did not acquire statistical significance in our study were total AE-QoL score and absolute number of basophils. However, these variables were considered fundamental by Sabaté-Brescó et al.[7] It is curious that these variables consider not only the characteristics of the onset of symptoms of both AE or their situation before diagnosis, but also their evolution after reaching a correct maintenance treatment (measured by AE-QoL). These disease evolution data are important when evaluating differences.

A statistical tool has been created that allows us to take an important step in differentiating between these 2 highly similar entities that are generating so much controversy. It is a multiple logistic regression predictive model that provides power to the study. It uses a different vision than what has been done to date: this model allows, through an equation, clinicians to discern between 2 highly similar entities with excellent specificity and sensitivity. This method confirms a hypothesis raised by previous studies. In the future, external validation should be carried out with a larger number of patients using a partition validation strategy, 20% to 80%, as well as a real-life application of the model.

In conclusion, CHA has similar characteristics to AE-CSU, although in general, episodes of AE are less frequent throughout the year, and they differ in their oropharyngeal location. However, a multiple logistic regression model has been created, using 7 clinical and evolutionary characteristics of both types of AE (CHA and AE-CSU), which, with high sensitivity and specificity, helps differentiate the 2 pathologies from each other, and determines that these 2 entities are independent.

DISCLOSURE STATEMENT

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Key messages

- **There is a lack of consensus defining CHA either as a separate acquired AE or as an endotype of CSU. A recent study suggests the existence of certain characteristics that would consider them to be different.**
- **A predictive model has been created that allows us to discern, using 7 clinical and evolutionary characteristics of both types of AE (CHA and AE-CSU), between 2 highly similar entities with high specificity and sensitivity.**
- **Our work supports the hypothesis published in previous studies that CHA and CSU should not automatically be considered the same disorder.**

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