ORIGINAL ARTICLE

Demographic and clinical characteristics of chronic histaminergic angioedema and chronic urticaria with angioedema, a multicenter Italian experience

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Summary

Background. Chronic spontaneous urticaria (CSU) is a common disorder characterized by the recurrence of wheals and/or angioedema for more than 6 weeks. About 35% of patients experience wheals and angioedema (AE-CSU) and around 6% of patients only present angioedema, also known as chronic histaminergic angioedema (CHA). As few data comparing CHA and AE-CSU are published, we analyzed the differences between demographic and clinical characteristics of these populations. **Methods.** A multicenter, observational, retrospective study, involving eight Allergology Centers in Lombardy, Italy, including 44 CHA and 34 AE-CSU pediatric and adult patients was performed. Data about sex, age, comorbidities, inflammatory markers, complement fractions, blood count, use of ACE inhibitors or angiotensin receptor blockers, site of angioedema attacks, therapy used to treat attacks, frequency of attacks at diagnosis, after 6 months of therapy and after 12 months of therapy were collected and analyzed. **Results.** A higher rate of atopy was found in AE-CSU than in CHA (58.8% *vs* 29.5%, $p = 0.01$). Hypothyroidism and antithyroid antibodies were more frequently detected in AE-CSU ($p < 0.05$). Face was the site majorly involved in both populations. Tongue angioedema was more reported in CHA than AE-CSU (22.7% *vs* 2.9%, $p = 0.019$). In CHA patients, upper airway involvement was reported mainly in male patients ($p = 0.02$). Monthly frequency of angioedema attacks at diagnosis was higher in AE-CSU than in CHA (2.1 *vs* 1.45, $p = 0.045$). **Conclusions.** Some characteristics may differentiate CHA from AE-CSU, as the latter experience higher rates of atopy, hypothyroidism and anti-thyroid antibodies positivity, as well as higher frequency of attacks and less tongue involvement.

Key words

Chronic spontaneous urticaria; chronic histaminergic angioedema; angioedema; wheals.

Introduction

Angioedema is a self-limited swelling of subcutaneous and submucosal tissues due to increased vasopermeability (1). A recent classification divided angioedema syndromes into five types: mast cell-mediated, bradykinin mediated, vascular endothelium dysfunction, drug induced and unknown aetiology (2). It is widely known that mast cell-mediated angioedema (AE-MC) might present in chronic spontaneous urticaria (CSU) (3), that is recurrent wheals and/or angioedema for more than 6 weeks (4). About 35% of patients with CSU feature angioedema with wheals (AE-CSU), whereas 6-10% of patients with CSU are characterized by angioedema without wheals (5, 6). The latter is also often termed as chronic histaminergic angioedema (CHA) (7-9). CHA is self-limiting and can be controlled by the administration of antihistamines, corticosteroids, adrenaline and/or omalizumab (10, 11). Several studies about CHA have been published in recent years (12-16) and some have looked at the clinical differences between patients with CHA and patients with AE-CSU (17-21).
We performed a multicenter, observational, retrospective study in Northern Italy in order to assess the clinical and epidemiological features of patients affected by CHA and AE-CSU.

Materials and methods

The present study involved eight Allergology Centers in Lombardy, Italy, and included both pediatric and adult patients affected by CHA and AE-CSU. Pediatric patients were two in each group. Data were anonymized and every patient gave an informed consent to participate in the study. Ethical approval was not required for this study involving anonymized clinical records collected retrospectively and analyzed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Patients presenting recurrent angioedema with or without wheals for more than 6 weeks and whose angioedema attacks responded to antihistamines, corticosteroids and/or omalizumab were included. Low C1-inhibitor levels were considered an exclusion criterion.
Forty-four patients with CHA and thirty-four patients with AE-CSU were included. Recorded data included: a) comorbidities (allergies, cancer, infections, cardiovascular diseases, respiratory diseases, endocrinological diseases), b) use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), c) blood count, d) complement fractions, e) autoantibodies, f) inflammatory markers, g) location of attacks and frequency of attacks at the moment of diagnosis, after 6 months and after 12 months.
Every patient underwent a complete physical examination.

Statistical analysis was performed using SPSS Statistics version 29. Quantitative variables are reported as means with standard deviation in brackets. Comparisons were carried out using the Student t test. Qualitative variables are reported as total number or percentage and comparisons were carried out using the Fisher exact test or the Chi-squared test when appropriate. Values were interpreted as significant with $p<0.05$.

Results

Study population demographics and characteristics

The mean age was slightly but not significantly higher in CHA than AE-CSU patients (53.3 vs 47.2 years). Median age was respectively 61 vs 49. The male/female ratio did not differ between the two populations (0.76 vs 0.7 in CHA and AE-CSU, respectively).
Atopy (allergic rhinitis, asthma or atopic dermatitis) prevailed in AE-CSU patients (58.8% vs 29.5%, $p=0.01$), as did the prevalence of hypothyroidism (29.4% vs 11.4%, $p=0.045$). As for other comorbidities, including Helicobacter pylori (HP) infection, no significant difference was detected. HP infections in both populations were treated with no angioedema and/or urticaria improvement. Population demographics and comorbidities are reported in Table I.

In both populations most patients on ACEi and ARB were shifted to another drug (four CHA patients and four AE-CSU patients), except for one patient who was kept on ARB and another who was shifted from ACEi to ARB (both in the AE-CSU population). Nonetheless, no angioedema improvement was recorded after 6 months. No use of gliptins was reported.
In the CHA group one patient reported the occurrence of angioedema attacks with non-steroidal anti-inflammatory drugs (NSAIDs) and one patient reported physical activity (cholinergic angioedema) and emotional stress as triggers for the onset of angioedema attacks. In the AE-CSU group a case of exacerbation with NSAIDs and two cases of delayed pressure angioedema were noted.

Blood tests

Blood eosinophilia and blood markers are reported in Table I. A significantly higher proportion of patients tested positive for anti-thyroid antibodies (anti-thyroperoxidase and anti-thyroglobulin) in the AE-CSU group compared to the CHA group (26.5% vs 6.8%, p=0.026). The remaining parameters did not differ between the populations. In both groups thyroid autoantibodies were detected in female patients only (20.4% of patients in CHA and 35.3% of patients in AE-CSU); $p<0.01$ vs male patients. Moreover, in both groups inflammatory markers were more elevated in the female population. In the CHA group, elevated ESR values, considering age and sex, were present only in the female population ($p<0.05$). In the AE-CSU population, females showed more frequently elevated CRP and/or ESR than male patients (50% vs 7.1%; $p<0.05$).
D-dimer was not measured systematically in this study; one female patient in the CHA group reported an elevated D-dimer value (597 µg/L) during an angioedema attack-free period.

Characteristics of angioedema attacks and therapy

The most frequent location of angioedema attacks was face (95% in CHA patients and 94% AE-CSU patients). Tongue angioedema was significantly more frequent in the CHA group than in the AE-CSU group (22.7% vs 2.9%, p=0.019). No significant differences between the two groups were recorded for other locations. One abdominal attack was reported by a patient in the AE-CSU group. In the CHA population, the upper airway involvement affected more men than women (50% vs 16%, p=0.02). No deaths were recorded.
Regarding the frequency of angioedema attacks at the time of diagnosis, the AE-CSU group reported a higher mean frequency of attacks than the CHA group, [2.1 (±1.82) vs 1.46 (±0.93) attacks/month (p=0.045), respectively]. We also considered the frequency of attacks after 6 months and after 12 months of therapy. We could not collect data of all patients, as, at the time of data collection, some were newly diagnosed and others were lost to follow-up. At both 6 months and 12 months, no statistically significant difference was detected between the two groups, who reported similar mean monthly attack frequencies. Data about attack locations and frequency of attacks are reported in Table I.
As shown in Table II, in the AE-CSU group the mean monthly frequencies of attacks in patients with or without cardiovascular comorbidity were significantly more frequent in the former [3.19 (±2.46) vs 1.51(±0.99), respectively; p=0.008]. No difference regarding angioedema locations was detected.
No differences in attacks frequency were recorded by sex, age, atopy, autoimmunity, other comorbidities, or inflammatory markers.
100% of patients in both populations were prescribed antihistamines, on demand (11.9% in CHA and 8.8% in AE-CSU) for less symptomatic patients or continuously up to fourfold the standard dose. Exactly 35.3% of patients in the AE-CSU group and 34.1% of patients in the CHA group used short oral corticosteroid courses on demand in addition to preventive therapy. As some patients did not achieve disease control (similar attack frequency and impactful symptoms on daily life) with antihistamines, therapy was implemented with omalizumab, tranexamic acid or hydroxychloroquine in 26.5% of AE-CSU patients and in 22.7% of CHA patients.
The frequency of angioedema attacks in patients treated with antihistamines alone or in association with corticosteroids and patients who implemented their therapy with omalizumab, tranexamic acid or hydroxychloroquine was compared. As displayed in Table III, a significant difference was found within the CHA population, as the former group experienced less attacks at diagnosis (1.27 vs 2.1, p=0.011) and at 12 months (0.18 vs 0.57, p=0.028). One patient on omalizumab did not optimally respond to such prophylactic therapy, however, no attempt at increasing the dose was tried. No significant difference was found in the AE-

CSU population. No significant difference in response between omalizumab, tranexamic acid and hydroxychloroquine evaluated singularly was recorded.

Discussion and conclusions

Chronic histaminergic angioedema is a common form of recurrent angioedema without wheals (3, 10). The treatment is the same recommended for CSU, with response to antihistamines and/or omalizumab (though not specifically licensed for CHA) as a means to diagnosis (4, 11). Some data providing new insights into clinical features and highlighting the differences between CHA and AE-CSU have been recently published (17-19, 21).

In our series, the male/female ratio did not differ between the two populations, with a higher female prevalence, as previously observed (12, 13, 20) but that was lower than the one reported for CHA by Faisant et al. (14) and Zajac et al. (15). Other authors found a significantly higher male/female ratio in CHA than in AE-CSU (18, 19, 21). As a matter of fact, considering all types of CSU, female patients are almost two times more frequent than male patients (22-24). Mean age was slightly older in CHA than in AE-CSU, unlike previous reports (18, 21).

Atopy was significantly more prevalent in AE-CSU patients. Some previous studies (15, 16), but not others (18-21), reported a higher prevalence of atopic disorders in CHA.

Most patients on treatment with either ACEi or ARB did not show any improvement after withdrawal of these drugs. Along with the good response to antihistamines and corticosteroids recorded, we concluded these patients were not affected by drug-induced angioedema. This highlights the difficulty of the differential diagnosis between drug-induced and histaminergic angioedema (25).

In our study, autoantibodies were detected in females patients only ($p<0.01$), which is not surprising, as females are more at risk of autoimmune diseases (26). However, no systemic autoimmune diseases were reported. AE-CSU patients reported a significantly higher prevalence of hypothyroidism and antibody positivity than CHA patients. Although this was not recorded in other studies (18-21), CSU as a whole is frequently associated with thyroiditis and anti-thyroid antibodies (5, 6). ANA showed the same prevalence as the general population (27) and that found by other authors (19, 20), but lower than that found by others (18). CRP and/or ESR were elevated in 22.7% of CHA patients vs 32.4% of AE-CSU patients, mostly in females ($p<0.05$). Previous studies suggested that in CSU, ESR levels correlate with disease severity (28), but we were unable to confirm this observation. This result might imply an elevated level of immune activity and inflammation (18).

The face was the most involved site of angioedema in almost all patients in both groups (14-16, 18-21, 29) but we recorded a significantly more frequent involvement of tongue in CHA than in AE-CSU ($p=0.019$) (18, 21). In the CHA population a male prevalent involvement of upper airways was observed ($p=0.02$), which supports the finding of a French group (14). An unusual case of abdominal attack was recorded in AE-CSU. Although abdominal angioedema is predominantly reported in hereditary angioedema syndromes, rare cases of abdominal involvement are also described in histaminergic angioedema (30, 31).

We found a higher mean monthly frequency of attacks at diagnosis in AE-CSU than in CHA, confirming a more severe phenotype of disease in AE-CSU than in CHA patients (17, 20, 21). Such difference was lost at 6 months and 12 months suggesting the effectiveness of the therapeutic intervention.

In AE-CSU patients, those affected by cardiovascular diseases (mainly hypertension) showed a higher prevalence of attacks at diagnosis. Buttgereit et al. reported a higher occurrence of metabolic diseases in patients affected by angioedema (21), and hypertension and metabolic disorders are frequent comorbidities in CSU (32, 33) that can be associated with a more severe disease (34). Since evidence suggests that CSU is characterized by systemic inflammation (35), it could be hypothesized that the additional inflammation caused by cardiovascular diseases may contribute to a more severe disease phenotype.

In both groups some patients did not respond optimally to antihistamine prophylactic treatment. Although short cycles of corticosteroids may be beneficial to the control of the disease (36), prolonged treatments with corticosteroids should be avoided, particularly in relatively young populations. Thus, the use of other preventative treatments should be considered. In CHA, attacks were significantly more frequent in those requiring an additional treatment at diagnosis ($p=0.011$) and after 12 months ($p=0.028$). No associations with biomarkers or comorbidities was detected. It should be stated that, as omalizumab is recommended for CSU

(4), the use of tranexamic acid and hydroxychloroquine may lie on single centers' experience. Overall, satisfactory responses were observed across all therapeutic groups: antihistamine prophylaxis, tranexamic acid, hydroxychloroquine and omalizumab. Only one patient reported almost no response to omalizumab, recording after one year a similar attack frequency to that of diagnosis. As recently stated by Zuberbier et al., the need for personalized treatment and disease-modifying drugs in CSU is still relevant (37). As a matter of fact, the current use of the term AE-MC highlights the contribution of mast cells' mediators (2). A recent review clarified the effect that mast cell degranulation exerts on the contact system, since degranulated heparin and polyanions may contribute to the activation of factor XII (38). In addition, the latest description of higher activation of the contact system in idiopathic angioedema (39) suggests a possible much larger role of the contact system in different types of angioedema. Importantly, the activation of the intrinsic coagulation pathway may contribute to CSU pathogenesis (40), remarking the inhibitory effect of tranexamic acid.
The limitations of this study are its retrospective nature, as some clinical information may be inaccurate and some patients were lost to follow-up, as well as the limited number of patients. No activity scores were employed and total IgE values were not available for every patient.

Diagnosing CHA requires a clinical approach based mainly on response to treatment to antihistamines, corticosteroids and/or omalizumab. Understanding demographic and clinical features may be of help to diagnose such condition and to provide the right therapy, since CHA is considered part of CSU.
When differentiating CHA from AE-CSU, some characteristics are more typically found in the former group as distinguishable features: higher male prevalence, older age, lower prevalence of hypothyroidism and anti-thyroid antibodies, tongue involvement, upper airways involvement in male patients, lower frequency of attacks, reduced signs and symptoms of atopy. Overall, prognosis is reassuring.
As diseases often have various presentations, it could be stated that CSU is a protean disorder with heterogeneous forms, ranging from only wheals to isolated angioedema (41). Thus, efforts pointing to characterize phenotypes and to a better understanding of the whole spectrum of CSU remain relevant.

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Contributions

S.S.: data curation, investigation, formal analysis, writing – original draft; F.R.: conceptualization, methodology, writing – original draft, supervision; A.T.: investigation, writing – review and editing; G.M., M.P., A.M.M., F.C., MR.Y., S.N., L.M., V.L., A.S., V.P.: investigation; R.A.: validation, visualization, writing - review and editing

All authors critically read and approved the final manuscript.

Conflict of interests

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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	CHA (n=44)	CSU-AE (n=34)	P value	Notes
***Sex** n (%)*				
Male	19 (43.2%)	14 (41.2%)		
Female	25 (56.8%)	20 (58.8%)		
M/F ratio	0.76	0.7	0.859	
***Age** (years) mean (std)*	53.3 (23.1)	47.2 (18.6)	0.217	
Range	3-88	8-88		
***Comorbidities** n (%)*				
Atopy (allergic rhinitis, asthma, atopic dermatitis)	13 (29.5%)	20 (58.8%)	**0.01**	
Cardiovascular disease	11 (25%)	12 (35.3%)	0.323	
Hypertension	10 (22.7%)	9 (26.5%)	0.703	
Respiratory disease	1 (2.3%)	0	1.000	
Endocrinological disease	10 (22.7%)	13 (38.2%)	0.136	
Hypothyroidism	5 (11.4%)	10 (29.4%)	**0.045**	
Helicobacter pylori infection	3 (6.8%)	5 (14.7%)	0.285	
Recurrent urinary tract infections	4 (9.1%)	2 (5.9%)	0.691	
Cancer	1 (2.3%)	1 (2.9%)	1.000	
***Eosinophilia** n (%)*	2 (4.5%)	1 (2.9%)	1.000	
***Autoantibodies** n (%)*	9 (20.4%)	12 (35.3%)	0.143	Autoantibodies positivity only in female patients (vs male patients, p<0.01)
ANA positivity	3 (6.8%)	4 (11.8%)	0.693	
Anti-thyroid antibodies	3 (6.8%)	9 (26.5%)	**0.026**	
Anti-phospholipid antibodies	1 (2.3%)	0	1.000	
Anti-mitochondrial antibodies	2 (4.5%)	0	0.502	
Anti-centromere antibodies	0	1 (2.9%)	0.436	
***CRP** n (%)*				Elevated values mostly in female patients (p<0.05)
Elevated values	8 (18.2%)	8 (23.5%)	0.562	
***ESR** n (%)*				
Elevated values	10 (22.7%)	7 (20.6%)	0.821	
***Location of attacks** n (%)*				Upper airway involvement mostly in male patients in CHA
Face	42 (95%)	32 (94%)	1.000	
Tongue	10 (22.7%)	1 (2.9%)	**0.019**	

Pharyngolaryngeal	10 (22.7%)	5 (14.7%)	0.373	(p<0.05)
Upper limbs	6 (13.6%)	5 (14.7%)	0.893	
Lower limbs	6 (13.6%)	5 (14.7%)	0.893	
Genitalia	2 (4.5%)	4 (11.8%)	0.395	
Frequency of attacks per month *(std)*				
At diagnosis				
At 6 months	1.45 (0.93)	2.1 (1.82)	**0.045**	
(n=35 for CHA, n=30 for CSU-AE)	0.58 (0.39)	0.44 (0.63)	0.291	
At 12 months				
(n=33 for CHA, n=26 for CSU-AE)	0.27 (0.45)	0.39 (0.72)	0.078	
Therapy *n (%)*				
Antihistamines	44 (100%)	34 (100%)	1.000	
Corticosteroids	15 (34.1%)	12 (35.3%)	0.912	
Omalizumab	6 (13.6%)	6 (17.6%)	0.626	
Tranexamic acid	4 (9.1%)	2 (5.9%)	0.691	
Hydroxychloroquine	0	1 (2.9%)	0.436	

Table I. Demographic characteristics, clinical features and blood markers of study populations.
Std=standard deviation, n=number of patients

	Patients with cardiovascular comorbidity	Patients without cardiovascular comorbidity	P value
Frequency of attacks per month *(std)*			
At diagnosis	3.19 (2.46)	1.51 (0.99)	**0.008**
After 6 months	0.68 (0.81)	0.29 (0.42)	0.092
After 12 months	0.39 (0.89)	0.37 (0.60)	0.925

Table II. Frequency of attacks per month between CSU-AE patients with cardiovascular comorbidity and CSU-AE patients without cardiovascular comorbidity.
Std=standard deviation

	Antihistamines with/without corticosteroids	Omalizumab or tranexamic acid	P value

Frequency of attacks per month *(std)*			
At diagnosis	1.27 (0.84)	2.1 (0.94)	**0.011**
After 6 months	0.56 (0.39)	0.64 (0.43)	0.664
After 12 months	0.18 (0.28)	0.57 (0.72)	**0.028**

Table III. Frequency of attacks per month between CHA patients treated with antihistamines with/without corticosteroids and CHA patients treated with omalizumab or tranexamic acid.
Std=standard deviation