



Angioedema Indicates a Different Endotype of Chronic Spontaneous Urticaria

Sinem ORNEK¹ , Emek KOCATURK² 

¹ Department of Dermatology, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

² Department of Dermatology, Koc University School of Medicine, Istanbul, Turkey

Corresponding Author: Emek Kocaturk ✉ ekocaturk@ku.edu.tr

ABSTRACT

Objective: Chronic spontaneous urticaria (CSU) is characterized by urticarial plaques and/or deeply seated swellings (angioedema) persisting for more than 6 weeks. Angioedema accompanies approximately half of CSU patients, however data on the clinical significance of angioedema is sparse. In our study, we aimed to investigate whether CSU cases accompanied by angioedema (CSUwAE) differ from CSU cases without angioedema (CSUwoAE) in terms of clinical features, treatment responses and associated conditions.

Materials and Methods: We retrospectively examined the medical records of chronic urticaria patients who were referred to the Urticaria Center of Reference and Excellence of Okmeydani Training and Research Hospital between January 2013 and July 2019, and included CSU patients who had at least 3 months of follow up data and Urticaria Control Test (UCT) scores at the 0 and 12th weeks in the study. We obtained demographic, clinical and laboratory characteristics of the patients and the treatments they received from the patient files. We evaluated the effectiveness of treatment using UCT. We compared data between CSUwAE and CSUwoAE cases.

Results: A total of 556 CSU patients were included in the study. Of all, 57% was CSUwAE and 43% was CSUwoAE. More CSUwAE patients had a disease duration of more than 5 years ($p=0.031$); and emergency admission, non-steroidal anti-inflammatory drug intolerance, autologous serum skin test positivity, and increased C-reactive protein values were found more frequently in CSUwAE cases ($p<0.001$; $p=0.011$; $p<0.001$; $p=0.009$, respectively). The skin prick test positivity rate was higher in CSUwoAE cases ($p=0.043$). The overall remission rates were lower in CSUwAE ($p=0.009$). Resistance to both standard doses of antihistamines and need for third-line treatments were more frequent in CSUwAE ($p=0.004$; $p=0.009$, respectively).

Conclusion: Angioedema is a feature of antihistamine refractory, severe CSU with longer disease duration and might be an indicator of autoimmune CSU.

Keywords: Angioedema, autoimmunity, autologous serum skin test, CRP, urticaria, treatment, biomarker

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by recurrent wheals and/or angioedema for longer than 6 weeks (1). It is estimated that 33-67% of CSU patients present with wheals and angioedema, while 29-65% exhibit only wheals (2,3). Angioedema is a non-pitting swelling of the deep dermis and/or subcutaneous tissue as well as mucous membranes at a deeper level than the wheal (4). Due to the pain or simply the disfiguring image it causes, angioedema may limit daily activities and negatively affects the quality of life of patients (5-7). CSU patients with angioedema may worry about experiencing life-

threatening airway obstruction due to swelling, and they refer to the emergency department more frequently than those without angioedema (6,7). Besides all of these, CSU presenting with both wheals and angioedema (CSUwAE) has been associated with longer disease duration, higher disease severity and antihistamine resistance compared to CSU without angioedema (CSUwoAE) (3,7,8). However, there is limited data regarding the differences between CSUwAE and CSUwoAE. Since the presence of angioedema causes differences in disease severity and treatment responses, whether CSUwAE is a different CSU endotype or whether angioedema is an independent risk factor for antihistamine resistance remains to be clarified.

In this study, we aimed to investigate the differences in demographic, clinical and laboratory characteristics and treatment responses between CSUwAE and CSUwoAE cases and we sought an answer to the question whether the presence of angioedema indicates a different endotype of CSU.

MATERIALS and METHODS

We retrospectively examined the medical records of CSU patients who were referred to the UCARE (Urticaria Center of Reference and Excellence) center of Okmeydani Training and Research Hospital between January 2013 and July 2019. We included CSU patients who had at least 3-month follow up data and Urticaria Control Test (UCT) score at the 0 and 12th weeks into the analysis. We excluded patients with acute urticaria, chronic episodic urticaria, isolated chronic inducible urticaria (CIndU), urticarial vasculitis, or isolated angioedema, and pregnant or breastfeeding patients as well as CU patients who had already received third-line treatment at the first referral from the study. We obtained the patients' age, gender, disease duration, accompanying CIndU, the presence of angioedema, emergency referrals, non-steroid anti-inflammatory drug (NSAID) intolerance, family history, chronic infection and stress history, in addition to the levels of total IgE, anti-thyroid peroxidase (anti-TPO) and C-reactive protein (CRP); the results of the skin prick test (SPT) and autologous serum skin test (ASST); and the prescribed treatments with dosages from patients' medical records. We divided the patients into two groups as CSUwAE and CSUwoAE according to the presence of angioedema. We then compared all patient features between the two groups.

We evaluated the treatment response using UCT, which assesses the control of signs and symptoms of the disease, quality of life impairment, efficacy of treatment, and overall disease control over the prior 4 weeks (9,10). Cases with an UCT score of ≥ 12 were considered as 'well-controlled' while < 12 was 'uncontrolled'. In addition, we defined the disease as 'in remission' if the CSU patients had UCT scores ≥ 12 for at least 12 weeks. We determined the treatments that provided remission in the patients, and classified them according to the treatment steps specified in the urticaria guidelines as follows (1,11):

- First-line treatment: Standard doses of second-generation antihistamines (sgAHs)

- Second-line treatments: Increased doses of sgAHs up to four-fold, combinations of two different groups of sgAHs, and combinations of sgAH with either first generation H1-antihistamines (fgAH) or leukotriene receptor antagonist (LTRA)

We defined patients who were unresponsive to both first- and second-line treatments as 'antihistamine resistant'. In addition, we compared the treatment steps that provided remission, and overall remission rates between the CSUwAE and CSUwoAE groups.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and the use of data for this study was approved by the local Ethics Committee of Istanbul Okmeydani Training and Research Hospital (163-2021).

Data Analysis

We performed statistical analysis using IBM SPSS Statistics for Windows v.21.0. (IBM Corp., Armonk, NY), and we presented categorical variables as frequencies and percentages, and quantitative variables as mean \pm standard deviation (SD) or median (range). We determined the normality of the distribution of numeric variables with the Kolmogorov-Smirnov test. To compare numeric and categorical variables between the CSUwAE and CSUwoAE groups, we used the Mann-Whitney U test and Pearson Chi-square test, respectively. We further analyzed the patient features found associated with angioedema with univariate analysis using the binomial logistic regression to determine whether they predict angioedema independently. We accepted the level of statistical significance at $p < 0.05$.

RESULTS

Study Population and Patient Characteristics

A total of 556 CSU patients were included in the study. There was a female predominance (71.8%) in the study population, and patients' age ranged from 11 to 85 years with a mean age of 39.76 ± 13.69 years. While 315 patients (56.7%) had accompanying angioedema, 241 patients (43.4%) had only wheals. The patients' clinical and laboratory features and the comparisons of them between CSUwAE and CSUwoAE groups are shown in Table I and II.

The increased CRP values and ASST positivity were associated with a higher likelihood of presenting angioedema in CSU patients (OR:2.35 [1.12-4.93], OR:2.96 [1.41-6.22], respectively).

Treatment Responses

We found that 37.1% of the CSUwAE cases and 49.4% of the CSUwoAE cases were in remission with standard doses of sgAHs ($p=0.004$). An additional 28.6% of the CSUwAE cases and an additional 26.6% of the CSUwoAE cases went into remission with second-line treatments. Antihistamine resistance was present in 34.4% of the CSUwAE cases and 24.1% of the CSUwoAE cases, and

they needed third-line treatment for symptom control ($p=0.009$). For further details, see Table III.

DISCUSSION

The clinical spectrum and treatment outcomes in CSU patients are variable. Being able to predict patients who are expected to have a severe, treatment-resistant and long-term disease when planning CSU treatment would contribute to both the physical and social well-being of patients and the economy of the country. Angioedema has become one of the many factors accused of being involved in clinical and prognostic variations of CSU, after its relationship with disease severity and duration and its negative impact on quality of life have been demonstrated (7).

Table I: Demographic and clinical characteristics of the patients.

Characteristics	All patients N=556, n (%)	Patients with CSUwAE N=315, n (%)	Patients with CSUwoAE N=241, n (%)	p value
Age (y), mean \pm SD; median; min -max	39.76 \pm 13.69; 39; 11-85	39.70 \pm 13.61; 39; 11-85	39.83 \pm 13.82; 40; 11-77	0.882 ^a
Sex; female	399 (71.8)	231 (73.3)	168 (69.7)	0.347 ^b
Duration of CSU (mo), mean \pm SD; median; min -max	32.86 \pm 54.89; 12; 1-480	35.76 \pm 61.51; 12; 1-480	29.07 \pm 44.63; 12; 2-240	0.892 ^a
Disease duration longer than 5 years	70 (12.6)	48 (15.2)	22 (9.1)	0.031^b
Accompanying CIndU	47 (8.5)	28 (8.9)	19 (7.9)	0.673 ^b
Emergency referrals	224 (40.3)	158 (50.2)	66 (27.4)	<0.001^b
Family history of CU	68 (12.2)	38 (12.1)	30 (12.4)	0.891 ^b
NSAID intolerance	41 (7.4)	31 (9.8)	10 (4.1)	0.011^b
Chronic infection	210 (37.8)	118 (37.5)	92 (38.2)	0.863 ^b
Stress	322 (57.9)	183 (58.1)	139 (57.7)	0.921 ^b
Baseline UCT score<12	391 (70.3)	229 (72.7)	162 (67.2)	0.161 ^b

^aMann Whitney U test, ^bPearson Chi-square Test, **CIndU**: Chronic inducible urticaria, **CU**: Chronic urticaria, **CSU**: Chronic spontaneous urticaria, **CSUwAE**: CSU presenting with both wheals and angioedema, **CSUwoAE**: CSU presenting without angioedema, **NSAID**: Nonsteroid antiinflammatory drug, **UCT**: Urticaria control test.

Table II: Laboratory characteristics of the patients.

Characteristics	All patients n/N (%)	Patients with CSUwAE, n/N (%)	Patients with CSUwoAE, n/N (%)	p value
Anti-TPO positivity	65/388 (16.8)	36/214 (16.8)	29/174 (16.7)	0.967 ^a
Increased total IgE values (>100 IU/mL)	250/384 (65.1)	135/214 (63.1)	115/170 (67.6)	0.351 ^a
Increased CRP values (>5 mg/dL)	130/328 (39.6)	82/178 (46.1)	48/150 (32)	0.009^a
ASST positivity	154/339 (45.4)	106/197 (53.8)	48/142 (33.8)	<0.001^a
SPT positivity	103/279 (36.9)	51/160 (31.9)	52/119 (43.7)	0.043^a

^aPearson Chi-square Test, **anti-TPO**: Anti thyroid peroxidase antibody, **ASST**: Autologous serum skin test, **CRP**: C-reactive protein, **CSUwAE**: Chronic spontaneous urticaria presenting with both wheals and angioedema, **CSUwoAE**: chronic spontaneous urticaria presenting without angioedema, **SPT**: Skin prick test.

Table III: Remission rates with antihistamines, and treatments that provided remission.

	Patients with CSUwAE (N=315), n (%)	Patients with CSUwoAE (N=241), n (%)	p value
In remission	207 (65.7)	183 (75.9)	0.009^a
First-line treatment			
Standard dose sgAHs	117 (37.1)	119 (49.4)	0.004^a
Second-line treatments	90 (28.6)	64 (26.6)	0.599 ^a
2-fold up dosed sgAHs	43 (13.7)	31 (12.9)	
4-fold up dosed sgAHs	23 (7.3)	20 (8.3)	
Combined sgAHs	12 (3.8)	4 (1.7)	
Standard dose sgAHs + LTRA	2 (0.6)	4 (1.7)	
Standard dose sgAHs + fgAH	5 (1.6)	2 (0.8)	
Up dosed sgAHs + LTRA	2 (0.6)	1 (0.4)	
Combined sgAHs + LTRA	3 (1.0)	1 (0.4)	
Up dosed and combined sgAHs	0	1 (0.4)	
No remission with first- and second-line treatments	108 (34.3)	58 (24.1)	0.009^a

^aPearson Chi-square Test, **CSUwAE**: Chronic spontaneous urticaria presenting with both wheals and angioedema, **CSUwoAE**: Chronic spontaneous urticaria presenting without angioedema, **sgAHs**: Second generation H1-antihistamines, **LTRA**: Leukotriene receptor antagonist, **fgAH**: First generation H1-antihistamines.

One of the most important findings of our study was that longer disease duration was more frequent in patients with CSUwAE, consistent with prior studies (7,8,12). Also, emergency department referrals were more frequent in the CSUwAE group, suggesting that patients with angioedema are more likely to seek urgent healthcare management (7). These findings support the ASSURE-CSU study results, which evaluated the CSU disease burden and reported that angioedema both negatively affects the patients' quality of life and increases the economic burden. In fact, the ASSURE-CSU study demonstrated that angioedema has a significant effect on the Dermatology Life Quality Index total score, even after controlling for wheals and pruritus (13). Therefore, the elimination of angioedema should be one of the primary goals of CSU therapy.

Secondly, we found that increased CRP levels and ASST positivity were higher in CSUwAE patients compared to those with CSUwoAE. As already known, the symptoms of urticaria occur by the release of histamine and other pro-inflammatory mediators from activated skin mast cells and basophils. Although, the exact underlying mechanisms of mast cell and basophil activation in urticaria are not conclusively established, the presence of circulating autoantibodies in about 40% of CSU patients indicated that autoimmunity could play a role in the pathogenesis of urticaria (14). Over the past years, two types of autoimmune hypersensitivity have been hypothesized to be relevant for CSU. One of them is type I autoimmunity

(also called autoallergy) in which autoantigens (for example; thyroid peroxidase (TPO)) crosslink the IgE on mast cells and basophils and cause the release of vasoactive mediators. The other is type II autoimmunity in which IgG and IgM autoantibodies bind to IgE or FcεRI on mast cells and basophils and lead to degranulation (15). ASST is an *in vivo* screening test that evaluates autoreactivity. It shows the presence of potential autoantibodies or other soluble factors in the patients' serum involved in the degranulation of cutaneous mast cells, and it was defined as a feature of type IIb autoimmunity (1,16,17). Similar to our findings, Tedeschi et al. (18) and Nettis et al. (19) have observed that CSU patients with angioedema were more frequently ASST-positive than those without angioedema. Also, Tedeschi et al. (18) have reported a significant difference between the patients with angioedema and patients with isolated urticaria using the basophil histamine release assay, which is a confirmatory test showing the presence of functionally active histamine-releasing autoantibodies (20); they found that patients with angioedema had stronger serum histamine-releasing activity (18). Several clinical studies have shown the role of inflammation on CSU pathogenesis and the presence of high CRP levels in CSU patients, especially in patients with positive ASST (21,22). Moreover, elevated CRP levels are suggested to be higher in type II autoimmunity (17). Therefore, we thought that angioedema may be a clinical indicator of type II autoimmunity as we found that increased CRP

values and ASST positivity were associated with a higher likelihood of presenting with angioedema in CSU patients.

Thirdly, we found that SPT positivity was lower in CSUwAE compared to CSUwoAE. It has previously been demonstrated that approximately 25-58% of patients with CSU have allergen sensitivity by SPT, an *in vivo* test used to demonstrate evidence of allergen sensitivity (23). Recently, it has been stated that patients with CSU may contain heterogeneous subgroups regarding autoreactivity or allergen sensitivity based on the results of ASST and SPT (24). It has also been reported that both ASST(+) SPT(-) and ASST(+) SPT(+) CSU patients had a significantly higher frequency of angioedema compared to ASST(-) SPT(+) or ASST(-) SPT(-) CSU patients (25). This observation is in line with our findings.

Fourthly, we found that NSAID intolerance was higher in the CSUwAE patients compared to those with CSUwoAE. NSAID intolerance, which is generally observed as an exacerbation of CSU symptoms after NSAID ingestion, is present in up to 30% of CSU patients (1,26). ASST positivity was found in a very high proportion of patients with multiple NSAID intolerance (27-29). These observations suggest that autoreactivity may contribute to NSAID hypersensitivity in CSU patients. Therefore, the fact that we found both ASST positivity and NSAID hypersensitivity to be higher in CSUwAE reinforces our idea that angioedema is a clinical indicator of autoreactivity.

Finally, we found that resistance to both standard doses of sgAHs and to increased doses or combination of sgAHs were more frequent in CSUwAE. Published data on the association of angioedema with antihistamine resistance are conflicting (30). Since both increased CRP levels and ASST positivity were previously reported as factors that are associated with antihistamine resistance (22,31-33), we were curious about whether the autoimmunity contributed to antihistamine resistance we had seen in our CSUwAE cases. Interestingly, we found no difference between patients who were ASST positive and ASST negative or between patients with increased CRP values and normal CRP values regarding antihistamine resistance (data not shown). Therefore, the presence of angioedema may be an indicator of antihistamine resistance regardless of its underlying pathomechanism or it might solely be a sign of disease severity. This needs to be clarified by further studies.

Our study has some limitations. One of them was its retrospective nature. For this reason, we could not reach all patients' laboratory results, but missing cases could be ruled out as the number of remaining patients was high enough for comparison. Secondly, we were unable to present the baseline UAS7 to measure baseline disease severity because most of our patients did not have baseline UAS7 scores in their files. One reason for this was that the majority of the patients who applied to us had symptoms despite their treatment and refused to spend a week without treatment. Instead, we preferred to use UCT to measure disease control. In fact, changes in the UCT score were reported to be strongly associated with disease-specific assessments of changes in UAS7. The transition of UCT ratings from "poor control" to "well controlled" is also well suited to UAS7-based assessment of treatment response (34). Finally, the study was conducted at a UCARE center where mostly patients with inadequately controlled CSU were referred. And, the target population was CSU patients who were followed for at least 12 weeks and had UCT scores at 0 and 12 weeks; thus, the study may not reflect the entire population of CSU patients.

CONCLUSION

Since angioedema is associated with a longer disease duration and increased frequency of emergency admissions, it seriously affects the quality of life of the patients and increases the economic burden. Therefore, a prompt step advancement of treatment (ie; third step) should be made considering that these patients are more often antihistamine resistant. More frequent prevalence of ASST positivity and increased CRP levels suggest that angioedema might also be associated with Type IIB autoimmunity but this needs further clarification with future studies.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authorship Contributions

Concept: **Sinem Ornek, Emek Kocaturk**, Design: **Sinem Ornek, Emek Kocaturk**, Data collection or processing: **Sinem Ornek, Emek Kocaturk**, Analysis or Interpretation: **Sinem Ornek, Emek Kocaturk**, Literature search: **Sinem Ornek, Emek Kocaturk**, Writing: **Sinem Ornek**, Approval: **Emek Kocaturk**.

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