

Angioedema frequently occurs in cholinergic urticaria

Emilia Juliane Mellerowicz, MD, Aida Asady, MD, Marcus Maurer, MD, and Sabine Altrichter, MD



Clinical Implications

- Patients with cholinergic urticaria frequently display concomitant angioedema. The occurrence of angioedema is associated with systemic reactions. Accordingly, these patients need more focused attention, search for differential diagnosis, and standby emergency treatment.

TO THE EDITOR:

Cholinergic urticaria (CholU), a frequent skin disorder that affects up to 20% of young adults,¹ is characterized by itchy wheals that are induced by physical exercise and passive warming. The etiopathogenesis of CholU is still not fully understood, but several publications suggest that there are different subgroups of patients with CholU.^{2,3}

Angioedema (AE) is a common feature of chronic spontaneous urticaria (CSU). Two of 3 patients with CSU have recurrent AE.⁴ In CholU, single case reports^{5,6} have documented the occurrence of AE, mostly in severely affected patients. Thus, the prevalence and relevance of AE in patients with CholU remains largely unknown.

To address this gap of knowledge, we retrospectively analyzed the charts of 107 consecutive patients with CholU seen at the urticaria center of reference and excellence (UCARE) at the Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin. All patients had bona fide CholU, confirmed by provocation testing in unclear cases. Their charts were reviewed for clinical data such as onset of disease, trigger factors, occurrence of AE, systemic reactions, concomitant diseases, age, sex, and employment status.

Statistical analyses were performed using IBM SPSS Statistics 25 for Windows. The statistical significance of differences between patient groups was calculated using the χ^2 test or Fisher's exact test (for small sample sizes) for categorical values or the Mann-Whitney *U* test for metric values. $P < .05$ was considered to indicate a significant difference.

Of the 107 patients analyzed, 64% were female, and the mean age at onset of disease was 28 (± 13.77 standard deviation) years. Patients had a high rate of concomitant allergies (43%) and a mean total IgE of 276.11 (± 617.96) IU/mL. About a quarter (27%) of the 107 analyzed patients had experienced extracutaneous signs and symptoms, alone or in combination, including dizziness, dyspnoea, uncomfortable feeling, and palpitations. Importantly, 46% of our patients with CholU had experienced AE at least once (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

CholU patients with AE and CholU patients without AE were comparable in their demographic features (see Table I) and showed no difference regarding their prevalence of trigger factors (data not shown). There was no significant difference in the total

IgE serum levels between these groups (see Table I). CholU patients with AE, as compared with CholU patients without AE, had higher rates of concomitant allergies (53% vs 35%) and atopic dermatitis (16% vs 5%), but these differences were not statistically significant ($P = .053$ and $P = .058$, respectively). Their rates of allergic rhinitis (39% vs 28%, $P = .219$), asthma (10% vs 10%, $P = .981$), and contact allergies (4% vs 2%, $P = .462$) were similar.

Interestingly, we found that CholU patients with AE are significantly more likely to experience extracutaneous signs and symptoms than CholU patients without AE (68% vs 27%, $P = .001$). The most frequent reported extracutaneous reactions were dizziness in almost one quarter of the cases (22% vs 14% in CholU without AE; $P = .001$) and dyspnoea in 18% of the cases (vs 5% in CholU without AE; $P < .001$). For detailed information see Figure 1.

Furthermore, we found significant differences between CholU patients with or without AE regarding their duration of disease until first presentation in our UCARE center (70.6 ± 69.3 vs 34.6 ± 33.6 months, $P = .02$) and the employment status of the patients. Patients with CholU and AE seem to be significantly less employed (33% unemployment), compared with patients without AE (0% unemployment, $P = .020$).

Our findings show that AE is quite common in patients with CholU, with 1 in 2 patients with CholU being affected, and that AE in CholU is linked to high disease severity and long duration.

Our study did not show demographic differences between CholU patients with and without AE. This is in contrast to the report by Washio et al,⁶ who reported that AE in patients with CholU occurs mainly in female patients. The most likely explanations for this are the differences in the design and size of this study compared with ours, which included more than a hundred consecutive patients with CholU.

We previously reported that atopic predisposition, concomitant allergies, and elevated total IgE levels are common features of patients with CholU and linked to more severe CholU in a small patient cohort.⁷ The present large retrospective analysis also showed a trend toward these findings. In this study, CholU patients with AE exhibited higher rates of concomitant allergies, although results just missed significance. Possibly AE could be one of the aggravating factors that add to the higher disease severity in atopic patients with CholU, although this remains speculative, as AE had not been assessed in the previous study.⁷

The most important finding of our study is that the majority of CholU patients with AE (68%) also experience extracutaneous signs and symptoms. This link was already described in a few case reports.^{6,8} In our study, the most frequently reported extracutaneous signs and symptoms reported by CholU patients with AE were dizziness and dyspnoea, which were, overall, mild in our patients and did not result in emergency department visits. Nevertheless, these symptoms could still cause a strong impairment in the quality of life, and if the trigger is not stopped or these symptoms are not treated, these systemic symptoms could, in principle, lead to more severe reactions. The awareness and understanding of extracutaneous systemic reactions in patients with CholU are limited and should be addressed by further studies.

TABLE I. Comparison of ChoU patients with and without angioedema

Total number of patients (n = 107)	With AE n = 49	Without AE n = 58	P value
Gender (% females)	65.3	62.1	.729
Age at onset of disease (y), mean $\pm$ SD, n = 104	28.3 $\pm$ 13.9, n = 48	27.8 $\pm$ 13.8, n = 56	.672
Duration of disease until first visit (mo), mean $\pm$ SD, n = 104	70.6 $\pm$ 69.3 , n = 48	34.6 $\pm$ 33.6 , n = 56	.020
Concomitant allergies (%)	53.1	34.5	.053
Other forms of urticaria (%)	42.9	43.1	.980
Other diseases* (%)	40.8	29.3	.101
Extracutaneous signs and symptoms (%), n = 70	68.0 , n = 45	26.7 , n = 25	.001
Total IgE (IU/mL), mean $\pm$ SD, n = 54	367.2 $\pm$ 816.0, n = 29	170.5 $\pm$ 211.9, n = 25	.278
Unemployment (%), n = 43	33.3 , n = 30	0.0 , n = 13	.020[†]

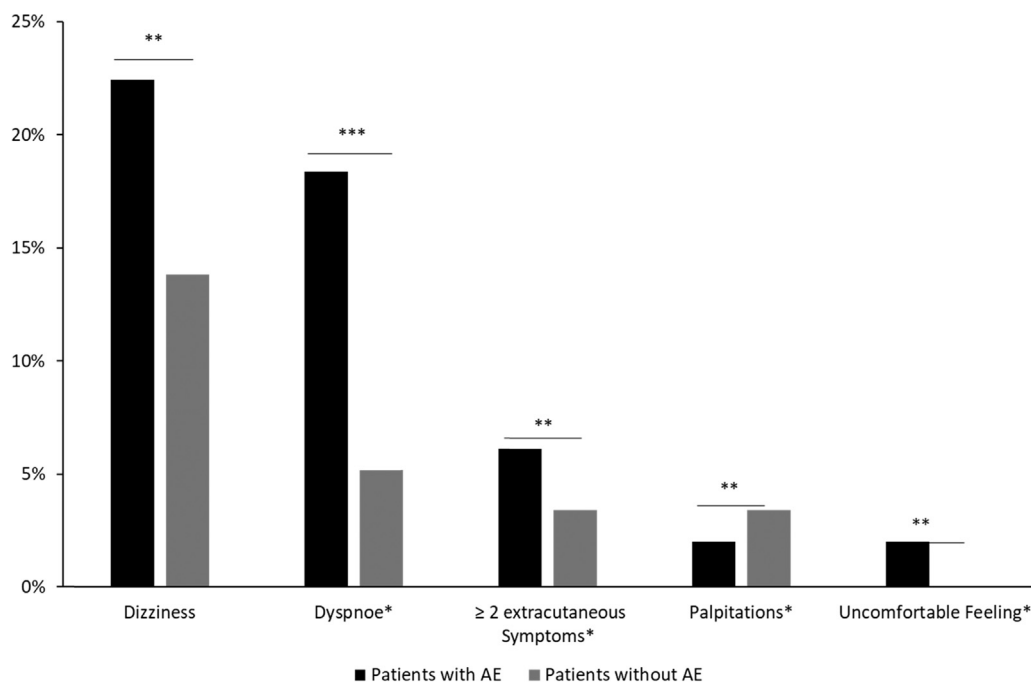
A total of 107 patients were analyzed. Percent or mean $\pm$ SD are given from patients where the information was available. If this was not calculated from all patients, patient numbers are displayed as "n" next to the results.

Bold indicates statistical significance ($P < .05$).

AE, Angioedema; ChoU, cholinergic urticaria; SD, standard deviation.

*Other diseases were mainly gastrointestinal (16.3% with AE, 3.4% without AE), psychiatric/psychosomatic (4.1% with AE, 8.6% without AE), and a broad variation of single cases of other diseases (eg, psoriasis, rosacea, acne, multiple sclerosis, hypertension, rheumatoid arthritis, diabetes, HIV).

[†]P value calculated with Fisher's exact test.



* P- value calculated by Fisher's exact test

FIGURE 1. Reported extracutaneous signs and symptoms in patients with AE (n = 49) and without AE (n = 58). Those symptoms were more frequent in patients with AE; only palpitations were significantly (P value = .009) more frequent in the group without AE (2% with AE, 3.4% without AE). ** $P < .01$; *** $P < .001$. AE, Angioedema.

Recurrent AE in ChoU appears to be linked to a longer disease duration, similar to CSU,⁹ although the underlying pathomechanism for this correlation is still unclear.

The higher rate of unemployment in ChoU patients with AE is possibly explained by their high disease severity and the higher prevalence of extracutaneous symptoms, which may lead to higher rates of absenteeism, causing problems at the workplace including unemployment.

It took ChoU patients with AE an average of 3 years before they presented to our UCARE. The reasons for this are unclear but may include high rates of delayed diagnosis or misdiagnosis, as AE and systemic reactions are not commonly considered to be clinical features of ChoU.

The strengths of our study include the relatively large patient population investigated and its rigorous characterization. As for limitations, this was a retrospective study in a selected patient

cohort of a tertiary center. In addition, patients had not been systematically assessed for disease activity, quality of life impairment, and treatment response. It would be interesting to assess the rates of CholU patients with recurrent AE as well as their treatment responses in a prospective study.

In conclusion, our findings show that many patients with CholU experience recurrent AE and that it is important to ask patients with CholU regarding AE. CholU patients with AE should be educated regarding their increased risk for systemic reactions, and further studies should aim to prospectively characterize the frequency, duration, localization, and the role and relevance of AE in CholU.

Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin, Berlin, Germany

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Corresponding author: Marcus Maurer, MD, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: marcus.maurer@charite.de.

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TABLE E1. Clinical characteristics of 107 CholU patient files, containing statement to AE

Item	Value
Gender (% females), n = 107	63.6
Age at onset of disease (y), mean $\pm$ SD (range), n = 104	28.1 $\pm$ 13.8 (6-71)
Duration of disease until first visit (mo), mean $\pm$ SD (range), n = 104	51.2 $\pm$ 55.8 (3-240)
Concomitant allergies (%), n = 107	43.0
Other diseases (%), n = 107	34.5
Concomitant other forms of urticaria (%), n = 107	43.0
Angioedema (% reported AE, at least once), n = 107	45.8
Extracutaneous signs and symptoms (% with extracutaneous signs and symptoms), n = 70	42.2
Total IgE, mean $\pm$ SD (range), n = 54	276.1 $\pm$ 618.0 (2-4376)
Unemployment (%), n = 43	23.3

A total of 93 analyzed patient files did not include a statement regarding AE. If not given else patient numbers are 107.

AE, Angioedema; CholU, cholinergic urticaria; SD, standard deviation.