

ORIGINAL ARTICLE

Atopic predisposition in cholinergic urticaria patients and its implications

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Abstract

Background Cholinergic urticaria (CholU) is a frequent chronic urticaria disorder with itchy weal and flare-type skin reactions in response to physical exercise or passive warming. A higher frequency of atopy among CholU patients has been reported, but the significance of this observation is unclear.

Objective To assess the prevalence and relevance of atopy in CholU patients.

Materials and Methods Thirty CholU patients were assessed for atopic skin diathesis (atopic predisposition) by use of the Erlangen Atopy Score and divided into atopic and non-atopic predisposed CholU individuals. Both groups were assessed for disease severity (CholUSI) and activity (CholUAS7), quality of life impairment [Dermatology Life Quality Index (DLQI) and CU-Q2OL], seasonal exacerbation, total and specific serum IgE and comorbidities.

Results CholU patients were found to exhibit high rates of atopic predisposition (57%), with higher prevalence and scores in female than in male patients. High Erlangen Atopy Scores were linked to high CholU severity, activity and impact on QoL. Atopic predisposed CholU patients show different seasonal exacerbation patterns, IgE specificity and comorbidity profiles as compared to non-atopic CholU patients.

Conclusion Atopic predisposition and cholinergic urticaria appear to be linked more closely than previously thought, which suggests shared pathogenetic mechanisms. Atopic patients with cholinergic urticaria have more severe disease and poorer quality of life than those who do not. Thus, all cholinergic urticaria patients should be assessed for atopic predisposition.

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Conflicts of interest

None.

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Introduction

Cholinergic Urticaria (CholU) is a frequent form of chronic inducible urticaria with itchy weal and flare-type skin reactions brought about by physical exercise or passive warming.¹ CholU affects up to 20% of young adults,² but only 0.2% of all dermatological patients present with CholU,³ indicating that most CholU patients do not seek the help of specialized physicians.

CholU is a chronic disease, usually lasting for several years, with a high impact on quality of life, as severely affected patients are not able to study, work or do housework.¹ CholU patients are considered to be hard to treat (Cases or case series:^{4–6}). For this disease, there are no specific therapies available. The current guideline (EAACI/GA²LEN/WAO/EDF urticaria guideline) recommends the use of antihistamines, but in many patients this

treatment does not lead to complete symptom control (Wosny *et al.*, manuscript in preparation).

The causes and pathomechanisms of CholU are largely unclear. Several theories have been proposed^{7,8} including: (i) a rise in core body temperature,⁹ (ii) occlusion of sweat pores or destruction of the sweat glands,^{7,8} (iii) mast-cell activation by acetylcholine and/or muscarinic receptor alterations,^{10,11} and (iv) hypersensitivity against sweat.^{7,8}

Back in 1967 Illig *et al.*¹² using serum-transfer experiments postulated CholU to be an antigen-antibody driven disease. Hirschmann *et al.*¹³ subsequently reported a higher frequency of atopy among his patients with CholU compared with the general population, and Adachi *et al.*¹⁴ showed that CholU patients develop weal and flare-type reactions when prick tested using

their own sweat, indicating a Type-I allergy against sweat. More recently, Hiragun *et al.*¹⁵ demonstrated IgE-driven hypersensitivity in CholU patients against a *Malassezia globosum* antigen in human sweat. *M. globosum* is a common lipophilic yeast found on the skin surfaces of many animals, including humans. Finally, the theory of CholU being an IgE-driven hypersensitivity reaction is strengthened by the finding that anti-IgE (Omalizumab) is a good therapeutic option in CholU patients.^{16,17}

In this study, we explored the prevalence and relevance of atopic predisposition with the help of the Erlangen Atopy Score, a summary score of clinical and cutaneous signs and symptoms of atopy, which is designed to measure atopic skin diathesis.¹⁸ On the basis of their atopy score values, we divided patients into atopic and non-atopic predisposed and explored them for differences.

Materials and methods

Patients

Thirty-five patients with a history of CholU¹⁹ were recruited at the Department of Dermatology and Allergy, Charité - Universitätsmedizin, Berlin. The presence of CholU was confirmed in 32 of these patients using pulse-controlled ergometry (PCE) provocation testing.²⁰ Of these, one patient withdrew consent and one took prohibited medication before testing and was excluded leaving 30 patients available for the statistical analyses. Of these 30 patients, 20 were female and their median age was 35 (range 19–76).

The study was approved by the Ethics Committee of Charité - Universitätsmedizin, Berlin (approval # EA4/124/10), registered with the German Clinical Trials Register (DRKS-ID: DRKS00004277) and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines, national laws and regulations as well as to the Standard Operating Procedures (SOPs) of the Allergie-Centrum-Charité at the Department of Dermatology and Allergy, Charité - Universitätsmedizin, Berlin. All participants gave signed informed consent at the beginning of the study.

None of the participants had taken systemic corticosteroids or applied topical antihistamines, corticosteroids or mast-cell stabilizers for 1 week, and all had stopped oral antihistamines at least 72 h prior to assessment.

Assessment of disease severity

Pulse-controlled ergometry (PCE) provocation testing²⁰ was used to verify the diagnosis of CholU and to determine disease severity. Briefly, patients performed a 30 min static bicycle ride in a pulse-controlled manner. Patients were instructed to speed up or slow down their pedalling speed to achieve an increase in pulse rate of 3 beats per minute to a final maximum of 160 beats per minute. The time to onset of wealing was recorded, as a

marker for disease severity. Observations were continued during a 10 min recovery period at the end of the 30 min of exercise.

The CholU severity index (CholUSI) was used to assess CholU severity.²⁰ The CholUSI is a sum score that takes into account the frequency of CholU symptoms (< once per month = 0; once a month = 1; > once a month = 2; once a week = 3; > once a week = 4; daily = 5; > daily = 6 points), eliciting factors (one point each for: physical exercise, hot bath, hot shower, emotional stress, hot food, sauna, other), duration of skin lesions (<5 min = 0; 5 to 10 min = 1; 10–20 min = 2; 20–30 min = 3; 30–60 min = 4; <1 h = 5 points) and itch (none = 0; mild = 1; moderate = 2; severe = 3 points). Accordingly, the CholUSI score ranges from 0 to 21 points: <5 points: very mild CholU; 5–9 points: mild CholU; 10–15 points: moderate CholU; >15 points: severe CholU.

Assessment of disease activity

In the daily diary, patients were asked to document their CholU signs and symptoms as well as trigger factors during the baseline and treatment phase. Specifically, patients recorded their itch intensity (Itchday: none = 0, mild = 1, moderate = 2, severe = 3) and their wealing intensity (Wealday: none = 0, mild = 1, moderate = 2, severe = 3) once daily in order to assess disease activity. Due to the fact that CholU patients usually exhibit pinpoint sized weals that are difficult to count, patients globally rated their wealing intensity instead of counting weal numbers as it is done in chronic spontaneous urticaria.²¹ In addition to itch and weals, patients were also asked to document, once daily, the exposure to elicitors of symptom development, for example, physical exercise, and the intensity of the elicitor they were exposed to (Intensity of elicitor day: no exposure to elicitors = 4, exposure to mild elicitor = 3, exposure to moderate elicitor = 2, exposure to strong elicitor = 1). The CholUAS7 was calculated as 7-day sum of [(Wealday + Itchday) x Intensity of elicitor day], reaching a maximum of 168 points. Comparisons of different composite scores have identified this score as best score for determining CholU disease activity (Wosny *et al.*, manuscript submitted).

Quality of life instruments

Quality of life was assessed using the Dermatology Life Quality Index (DLQI) questionnaire²² and the Chronic Urticaria Quality of life questionnaire^{23,24} following recent recommendations.²⁵ The DLQI measures skin health-related quality of life, has a recall period of 7 days, consists of 10 questions and has a score that can range from 0 to 30, with 0–1 points: no impairment, 2–5 points: low impairment, 6–10 points: moderate impairment, 11–20 points: strong impairment and >20 points: extreme impairment. The German CU-Q2oL assesses disease-related QoL in six dimensions (functioning, sleep, itching, mental status, swelling/eating and limits looks). It has 23 questions, each of them answered with a five-level Likert scale. The total Cu-Q2oL

score ranges from 0 to 100, with higher score values indicating higher quality of life impairment.

Assessment of atopy

Atopic predisposition was investigated using the modified Erlanger Atopy score questionnaire according to Diepgen *et al.*¹⁸ This questionnaire determines anamnestic and present atopic stigmata (such as flexural eczema, cradle cap, itch upon sweating, textile and metal intolerance, xerosis, pulpitis sicca, earlobe fissures, Hertoghe sign, white dermatographism etc.), includes family history and total IgE levels in order to assess a likelihood of (skin) atopic diathesis (for the used German version see: http://www.diss.fu-berlin.de/diss/servlets/MCRFileNodeServlet/FUDISS_derivate_00000008330/Freund_Dissertation.pdf²⁶). The scoring system for this questionnaire is Category 1, no atopy (Score 0–3 points); Category 2, atopy unlikely but cannot be excluded (score 4–9 points); Category 3, atopic (score 10–14 points); Category 4 severely atopic (score >14 points).

For a laboratory assessment of atopy, patient serum was collected by venous puncture and sent to the central laboratory of the clinic: Labor Berlin, Berlin, Germany. Using the ImmunoCAP System Phadia Laboratory Systems, Thermo Fisher Scientific Inc, Uppsala, Sweden, the following parameters were determined: (i) total IgE (ii) inhaled allergen mix SX1 (Timothy g6, Rye g12, Birch t3, Mugwort w6, Cat Dander e1, Dog Dander e5, Cladosporium herbarum m2 and Dermatophagoides pteron d1) (iii) perennial environmental allergens (*Dermatophagoides farinae* (d2), *Dermatophagoides pteron.* (d1)).

Statistical analyses

Data are presented as mean $\pm$ SEM. The statistical significance of differences between patients groups was calculated using Student's *t*-test for independent means and the Fishers exact test. Correlations were calculated using the Spearman's rank test. $P < 0.05$ was considered to indicate a significant difference.

Results

All but one of our 30 patients were at least moderately or severely affected as assessed by the CholUSI (mean 14.6 ± 0.4). The median of duration of CholU was 5 (1–43) years, and the mean CholUAS7 score was 43 ± 5 , indicating high disease activity. The mean number of attacks per week was 5.4 ± 0.4 with a mean duration of wealing of 1.5 ± 2.3 h. Patients' quality of life was markedly impaired, with a mean DLQI score of 9.7 ± 1.1 and a mean CU-Q2oL score of 52 ± 3 .

Atopic predisposition is frequent in CholU patients, especially in female CholU patients

As assessed by the Erlangen Atopy score, 17 of the 30 CholU patients (57%) were found to be atopic (Category 3 or 4), four of them severely atopic (Category 4). For further analyses these were designated as atopic predisposed CholU (apCholU)

patients. The remaining 13 patients (43%) fell into Category 2 (atopy unlikely but cannot be excluded) and were designated as non-atopic predisposed CholU (napCholU) patients. The rate of atopy was significantly higher in CholU patients ($P < 0.001$, Fig. 1) as compared with healthy German individuals.²⁷ Interestingly, 15 of the 17 apCholU patients (88%) were women ($P = 0.007$, Fig. 2) and women had a significantly higher mean atopy score (13.2 ± 1.2) than men (7.6 ± 0.8 ; $P = 0.005$).

Disease activity, severity and annual variability in apCholU and napCholU patients

Mean disease activity scores (CholUAS7, Fig. 3) indicated that apCholU patients (53 ± 8) are significantly ($P = 0.029$) more affected than napCholU patients (30 ± 4). Also, CholUAS7 scores were positively correlated with the Erlangen atopy scores

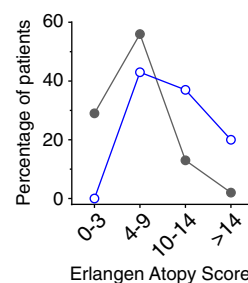


Figure 1 Atopy is more frequent in CholU patients than healthy German individuals. The Erlangen atopy scores of the 30 CholU patients (blue symbols) is compared with a historical group of 2176 healthy young German persons.²⁶ The distributions are significantly different (chi-squared test $P < 0.001$). Erlangen atopy scores are divided into: Category 1 (Score 0–3 points): no atopy; Category 2 (score 4–9 points): atopy cannot be excluded; Category 3 (score 10–14 points): atopic; Category 4 (score >14 points): severely atopic.

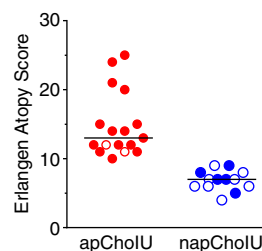


Figure 2 Distribution of Erlangen atopy scores among the 30 CholU patients. Those with atopy scores ≥ 10 were designated atopic (apCholU) (red circles) and those with scores ≤ 9 , non-atopic (napCholU). Horizontal lines indicate median values. The solid circles indicate females and the open circles males. In the apCholU group, females outnumber males' 15:2 while in the napCholU, the ratio was 5:8. This difference was statistically significant ($P = 0.007$, Fisher's exact test).

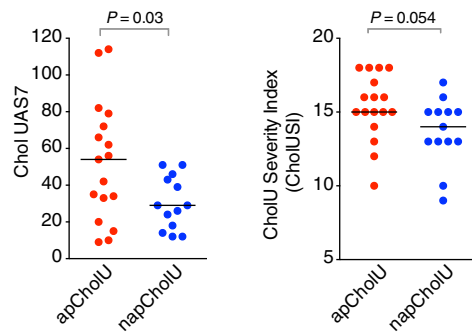


Figure 3 apCholU patients (red circles) have more disease activity (CholUAS7) and are more severely affected (CholU Severity Index) than napCholU patients (blue circles). Horizontal lines indicate median values.

($r = 0.40$, $P = 0.028$, data not shown). Although severity scores assessed by CholUSI were higher in apCholU patients (15.4 ± 0.5) than in napCholU patients (13.7 ± 0.6) (Fig. 3), the difference was not statistically significant ($P = 0.054$). However, CholUSI scores were significantly correlated with the Erlangen atopy scores ($r = 0.41$, $P = 0.025$, data not shown).

Quality of life was also more seriously affected in apCholU patients than in napCholU patients (Fig. 4). The mean DLQI scores in apCholU and napCholU patients of 11.8 ± 1.7 and 7.0 ± 0.9 , respectively, were significantly different ($P = 0.03$). Similarly, the mean CU-Q2oL scores in apCholU and napCholU patients were significantly different (58 ± 4 vs. 45 ± 3 , $P = 0.03$).

Although not statistically significant, there were small trends suggesting that patients with apCholU experience more severe disease following provocation than those with napCholU. In the pulse-controlled ergometry test, the mean time for the development of symptoms was 9.2 ± 2.3 min for apCholU patients

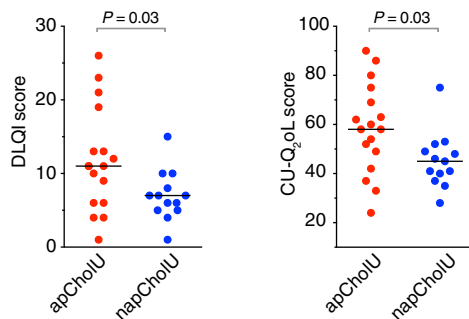


Figure 4 apCholU patients (red circles) have a significantly poorer quality of life, as assessed by both DLQI and CU-Q2oL, than napCholU patients (blue circles). Horizontal lines indicate median values. DLQI, Dermatology Life Quality Index.

compared with 12.3 ± 3.0 min for napCholU patients (data not shown).

Differences in seasonal exacerbation, IgE specificity and comorbidities between atopic and non-atopic predisposed CholU patients

There was a marked difference between apCholU and napCholU patients with respect to the time of year when their disease was most active (Fig 5). Of the apCholU patients, almost half (47%) reported that their CholU is worst in the summer, whereas only one (6%) was worst in winter. In contrast, summer was the worst season for only 25%, but winter was the worst season for 46% of napCholU patients.

Of the 30 CholU patients, 15 (50%) had elevated total serum IgE levels, that is, >100 kU/mL (Table 1). Rates of elevated IgE and mean IgE levels were higher than normal in both atopic and non-atopic predisposed CholU patients. Approximately half of CholU patients had sIgE to seasonal inhaled allergens and slightly less to perennial allergens, with no difference between atopic and non-atopic predisposed CholU patients.

The prevalence of concomitant allergic diseases in the CholU patients are shown in Table 2. Thirteen per cent of the CholU patients reported atopic dermatitis or allergic asthma and 20% allergic rhinoconjunctivitis. apCholU and napCholU patients did not differ in their rates of atopic dermatitis, allergic asthma

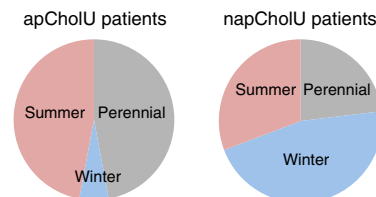


Figure 5 Seasonal distribution of CholU aggravations. The colour codes are: pink, summer; blue, winter; and grey, perennial.

Table 1 Percentage of patients with elevated IgE levels

Patients with elevated serum sIgE levels (%)	All CholU patients (n = 30) (%)	apCholU patients (n = 17) (%)	napCholU patients (n = 13) (%)	P-value*
Total IgE	50	53	46	n.s.
Inhalation mix (SX1:g6,g12,t3,w6,m2,d1,e1)	53	59	46	n.s.
<i>Dermatophagoides farinae</i>	40	47	31	n.s.
<i>Dermatophagoides pteron.</i>	37	41	31	n.s.

*Indicates significance between apCholU and napCholU patients. apCholU patients, atopic cholinergic urticaria patients; napCholU patients, non-atopic cholinergic urticaria patients; n.s., not significant.

Table 2 Concomitant diseases in CholU patients. Patients were assessed for comorbidities by use of a checklist

Concomitant diseases	Number of patients (n = 30) (%)	apCholU patients (n = 17) (%)	napCholU patients (n = 13) (%)	P-value*
Atopic dermatitis	13	18	8	n.s.
Allergic asthma	13	18	8	n.s.
Allergic rhinoconjunctivitis	20	18	23	n.s.
Contact allergy (Type IV hypersensitivity)	20	29	8	<0.01
Chronic inducible urticaria	20	29	8	<0.01
Thyroid disease	13	18	8	n.s.
Arterial hypertension	10	12	8	n.s.
Rheumatoid arthritis	10	6	15	n.s.
Other	43	59	62	n.s.

*Indicates significance between apCholU and napCholU patients.
n.s., not significant.

or allergic rhinitis. However, significantly more apCholU patients reported contact allergies (type IV hypersensitivities) (29% vs. 8%, $P < 0.01$) and concomitant chronic inducible urticaria, such as cold contact urticaria or symptomatic dermographism (29% vs. 8%, $P < 0.01$).

Discussion

Our study shows that patients with moderate to severe CholU show high rates of atopy and that apCholU patients are more severely affected and different from napCholU patients in their seasonal exacerbation patterns, IgE specificity and comorbidity profiles.

The rate of atopy, assessed by the Erlangen Atopy score, is higher in CholU patients as compared to healthy people. A high prevalence of atopy (34%) has been reported previously by Hirschmann *et al.* 1987,¹³ who considered patients atopic when they had a personal history of childhood eczema, hay fever or childhood asthma. Using the Erlangen Atopy Score, 57% of our patient population is atopic. This even higher prevalence of atopy might be due to the different assessment of atopy, the overall increasing prevalence of atopy^{28,29} or due to our selected patient population of rather severely affected patients.

Although cholinergic urticaria is often regarded among physicians as a 'young man's disease', Zuberbier *et al.* reported 1994² a higher prevalence in women (12%) compared to men (10%) among German pupils and students. Consistent with this report, we also found a higher prevalence of women among our study patients. Whether this is because women are more affected or more likely to seek medical help and to participate in clinical studies is not clear. Atopy was significantly correlated with female sex, which is consistent with the most recent German cohort study,²⁹ where women also had a higher prevalence of allergy compared to men.

To the best of our knowledge, populations of CholU patients have never been divided in those with and without an atopic disposition. When we did this using the Erlangen Atopy Score,¹⁸ allergic patients had significantly more contact allergy (Type IV hypersensitivity) and concomitant chronic inducible urticaria. Furthermore, allergic CholU patients had a poorer quality of life, greater disease activity and a tendency to have more severe disease.

Differences in seasonal exacerbation have been reported in Japanese CholU patients.^{30,31} In our CholU patient population, atopy was associated with disease exacerbation in the summer, which could be associated with seasonal contact of air borne allergens or with more frequent sweating. We anticipate that apCholU patients, where allergies and hypersensitivities could play a major role in the disease, are distinct to napCholU patients where other factors, such as blockage of the sweat glands (and matching aggravation in the winter) or acetylcholine/acetylcholine receptor aberrations could occur.^{7,32}

Elevated total IgE levels have been reported in chronic spontaneous urticaria.³³ While elevated total IgE levels in CholU due to increased frequency of atopy may be predicted, to the best of our knowledge, it has not been reported previously. Furthermore, studies on seasonal exacerbations^{30,31} have not investigated total or specific IgE serum levels. Surprisingly, not only the atopic but also the non-atopic CholU patients had high and comparable prevalences for elevated total IgE, sIgE to inhalant allergens and house dust mite. There could be several explanations for these results. First, it could indicate that CholU patients are in general 'allergy prone', which cannot be detected via the Erlangen Atopy score, which was originally designed for atopic skin diseases. Conversely, respiratory atopy could be missed. Second, elevated total IgE could be a sign of extrinsic reactivity to environmental allergies (classical atopy) but could also be a sign of intrinsic reactivity to autologous antigens as an 'autoallergy'. This concept has also been proposed for chronic spontaneous urticaria, where IgE to self has been detected.^{34–36}

The strength of this study is the detail with which we have examined our population of CholU patients. A weakness is that we used a patient questionnaire designed for atopic dermatitis to indicate an allergic disposition in our population, the Erlangen atopy score, currently the main tool available to determine if patients are atopic or not. The use of this questionnaire may be the reason that our apCholU patients had a significantly higher rate of Type IV contact allergies compared to napCholU.

In conclusion, atopy and cholinergic urticaria are linked more closely than previously thought. Shared pathogenic mechanisms are likely and should be characterized in future studies. Also, atopic patients with cholinergic urticaria have more severe disease and poorer quality of life than those who do not. Thus, cholinergic urticaria patients should be assessed for atopy.

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