


# Effects of Atopy and Allergen Types on Disease Course in Patients with Chronic Spontaneous Urticaria

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## ABSTRACT

**Objective:** Type I autoimmune response (autoallergic) and type IIb autoimmune response have been described in the pathogenesis of chronic spontaneous urticaria (CSU). However, the aetiology is still unknown. In this study, we aimed to investigate the frequency of atopy and the effects of atopy and allergen types on the course of the disease in patients with CSU.

**Materials and Methods:** The study included 261 CSU patients aged 18 years and older who underwent the aeroallergen skin prick test and/or serum-specific IgE test. Clinical and laboratory characteristics of the patients were compared according to the presence of atopy and the allergen types.

**Results:** According to aeroallergen-specific IgE, 89 patients (34.1%) were considered atopic. Female gender, thyroid autoantibody (TPO, Tg) positivity, and ANA positivity were significantly higher in the nonatopic group ( $p=0.002$ ,  $p=0.001$ ,  $p=0.008$ , respectively). Total IgE levels, and high total IgE and C4 level rates were higher in the atopic group ( $p<0.001$ ,  $p<0.001$ ,  $p=0.02$ , respectively). High total IgE (3.92-fold risk, 95% CI) and elevated C4 (2.41-fold risk, 95% CI) were independent risk factors for atopy. There was a significant difference in C4 levels between pollen and multiple sensitization groups ( $p=0.007$ ). No significant difference was found between the groups in terms of age, disease duration, presence of angioedema, sedimentation, CRP, C3 and antihistamine treatment response ( $p=0.13$ ,  $p=0.80$ ,  $p=0.68$ ,  $p=0.12$ ,  $p=0.93$ ,  $p=0.28$ ,  $p=0.58$ , respectively).


**Conclusion:** The findings suggest a possible association between atopy and chronic spontaneous urticaria, and that atopy may predispose to chronic urticaria. Patients with CSU can be classified as atopic and nonatopic (autoimmune), and this classification may be effective in determining the step treatment modality.

**Keywords:** Atopy, specific IgE, chronic urticaria

## INTRODUCTION

Chronic urticaria (CU), defined as urticaria and/or angioedema lasting longer than six weeks, is classified into two groups: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU). Inducible urticaria is characterized by specific triggers. Some patients may present with more than one subtype of urticaria (1,2). Angioedema is observed in 40% of patients (3). Although the pathogenesis of CSU is not clear, the main effector cells are mast cells, the basophils and B lymphocytes are involved in the pathogenesis. Mast cell activation caused by immunoglobulin E (IgE) autoantibody-mediated autoallergy

and immunoglobulin G (IgG) autoantibody-mediated autoimmunity is the mechanism defined in the pathogenesis of chronic spontaneous urticaria (4,5). However, the etiology is still not completely known (1). Recent studies have shown that atopy may predispose to CU. It has been reported that atopic diseases including allergic rhinitis, allergic conjunctivitis, asthma, and atopic dermatitis are frequently observed in patients with chronic urticaria, and allergen-specific IgE positivity is higher in patients with chronic urticaria compared to healthy controls. Different studies with different allergens show that house dust sensitization is remarkable (2,6-9).

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In our study, we aimed to investigate the frequency of atopy in patients with chronic spontaneous urticaria and the effects of atopy and allergen types on the course of the disease.

## MATERIAL and METHODS

The study included 261 CSU patients presenting to the Immunology and Allergy clinic between January 2018 and January 2025. Patients aged 18 years and older with chronic spontaneous urticaria for more than 6 months who underwent an aeroallergen skin prick test and/or serum specific IgE testing were included in the study. Patients with a history of active malignancy, chronic infection, rheumatological disease that may affect the course of the disease, and patients receiving immunosuppressive therapy or corticosteroid therapy for any disease other than CSU were excluded from the study.

Demographic characteristics such as age, gender, disease duration, presence of angioedema, and history of atopic disease (allergic rhinitis, asthma, atopic dermatitis, etc.) were recorded from the file information. According to the step treatment status (1), patients whose disease was controlled with antihistamine treatment were considered to show antihistamine treatment response, and patients receiving omalizumab treatment were considered to be antihistamine resistant. Laboratory findings including total IgE, aeroallergen specific IgE, complement 3 (C3), complement 4 (C4), anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-Tg), anti-nuclear antibody (ANA), sedimentation, and C-Reactive protein (CRP) were also recorded from the file information. Total IgE levels  $\geq 100$  IU/mL were considered high total IgE. At least 1 positive skin prick test with aeroallergens or positive aeroallergen serum-specific IgE was considered as atopy. Allergen types were determined according to the results of skin prick tests with aeroallergens. Clinical and laboratory characteristics of patients with and without atopy were compared, and clinical and laboratory characteristics were also compared according to allergen types in patients with atopy.

This study protocol was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee, (approval number: 2025/43). This study was conducted according to the ethical principles of the 1964 Declaration of Helsinki with its later amendments and comparable ethical standards.

The SPSS 22 program was used for statistical evaluation of the data. The data obtained were presented as mean  $\pm$  standard deviation, median (min-max) and percentage according to the distribution of the data. The Mann-Whitney U test, Student's t-test, Chi-square test and Fisher's exact test were used to analyse the data. Spearman or Pearson correlation analysis was performed according to normal distribution. Multivariate logistic regression analysis was performed to identify independent predictors of atopy. Variables considered clinically relevant and those showing an association in univariate analysis ( $p < 0.10$ ) were entered into the multivariate model as potential confounders. Age, sex, total IgE level, and C4 level were included in the final model. The goodness of fit of the model was assessed using the Hosmer-Lemeshow test. The data were analysed at a 95% confidence interval and a p-value less than 0.05 was considered significant.

## RESULTS

A total of 261 patients, 179 of whom were female (68.6%) with a mean age of  $38.67 \pm 12.95$  years, were included in the study. The median disease duration was 24 months (6-240). Angioedema was present in 43.3% and high total IgE ( $\geq 100$  IU/mL) was present in 50.4% of the patients. Thyroid autoantibody positivity was present in 23.4% of the patients and ANA positivity was present in 23% of the patients. Median sedimentation and CRP were 12 (1-65 mm/h) and 2 (1-52 mg/L), respectively. C4 was low in 9 patients, while C3 was not low in any patient. A history of atopic disease was present in 52 patients, including a history of multiple atopic diseases in some patient; 32 patients had allergic rhinitis (AR), 33 patients had asthma, and 1 patient had atopic dermatitis (AD). Antihistamine treatment response was present in 141 patients (54%). According to the results of the aeroallergen skin prick test and/or serum sIgE test, 89 patients (34.1%) were considered atopic (Table I).

When CSU patients with and without atopy were compared, female gender, thyroid autoantibody positivity, and ANA positivity were significantly higher in the nonatopic group ( $p=0.002$ ,  $p=0.001$ ,  $p=0.008$ , respectively). Total IgE levels, and high total IgE and C4 level rates were higher in the atopic group ( $p<0.001$ ,  $p<0.001$ ,  $p=0.02$ , respectively). High total IgE was identified as an independent predictor of atopy (OR: 3.92, 95% CI: 1.71–5.40,  $p < 0.001$ ). Similarly, elevated C4 levels were associated with an increased risk of atopy (OR: 2.41, 95% CI: 1.10–2.52,  $p = 0.02$ ). His-

**Table I:** Comparison of clinical and laboratory data in patients with atopic CSU and nonatopic CSU

	<b>Total n=261</b>	<b>Atopic CSU n=89 (34.1%)</b>	<b>Nonatopic CSU n=172</b>	<b>p-value</b>
Age, year, mean±SD	38.67±12.95	37.36±11.9	39.33±12.79	0.13
Female, n (%)	179 (68.6)	50 (56.2)	129 (75.0)	<b>0.002</b>
Disease duration, months, median (min-max)	24 (6-240)	24 (6-240)	24 (6-240)	0.80
Angioedema, n (%)	113 (43.3)	37(41.6)	76(44.2)	0.68
High total IgE (≥100 IU/mL), n (%)	123/244 (50.4)	63/87(72.4)	60/157 (38.2)	<b>&lt;0.001</b>
Total IgE (IU/mL), median (min-max)	98 (8-2926)	215(14-2926)	69(8-1887)	<b>&lt;0.001</b>
Thyroid autoantibody positivity, n (%)	58/248 (23.4)	10/87 (11.5)	48/161(29.8)	<b>0.001</b>
• Anti-TPO	37/248 (14.9)	6/87 (6.9)	31/161 (19.3)	<b>0.009</b>
• Anti-Tg	40/195 (20.5)	7/63 (11.1)	33/132 (25.0)	<b>0.025</b>
ANA positivity, n (%)	56/243 (23.0)	10/79 (12.7)	46/164 (28.0)	<b>0.008</b>
Sedimentation (mm/h), median (min-max)	12 (1-65)	11 (2-43)	13 (1-50)	0.12
CRP (mg/L), median (min-max)	2 (1-52)	2 (1-35)	2 (1-52)	0.93
C3 (mg/dl), mean±SD	130.28±22.75	132.98±18.49	129.45±24.57	0.28
C4 (mg/dl), mean±SD	27.36±8.91	29.08±8.99	26.46±8.77	<b>0.03</b>
Low C4, n (%)	9/236(3.8)	2/81(2.5)	7/155(4.5)	0.72
History of atopic disease, n (%)	52 (19.9)	35 (39.3)	17 (9.9)	<b>&lt;0.001</b>
• AR	32 (12.3)	31 (34.8)	1 (0.6)	<b>&lt;0.001</b>
• Asthma	33 (12.6)	17 (19.1)	16 (9.3)	<b>0.024</b>
Antihistamine treatment response, n (%)	141(54.0)	46 (51.7)	95 (55.2)	0.58

**Ig:** immunoglobulin, **TPO:** thyroid peroxidase, **Tg:** thyroglobulin, **ANA:** anti-nuclear antibody, **CRP:** C-reactive protein, **C:** complement, **AR:** allergic rhinitis, **min:** minimum, **max:** maximum

Data are presented as mean ± SD or median (min–max). Statistical analyses were performed using Student's t-test or the Mann–Whitney U test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables.

tory of atopic disease was significantly more common in the atopic group ( $p<0.001$ ) and no significant difference was found between the groups in terms of age, disease duration, presence of angioedema, sedimentation, CRP and antihistamine treatment response (Table I).

Of the 64 patients with atopy detected by skin prick test, 46 had sensitivity to a single type allergen (71.8%) and 18 had sensitivity to multiple types of allergen. Distribution of single type allergen positivity was 28 pollen (44.4%), 17 house dust (27%) and 1 mold, while multiple allergen positivity was 12 pollen + house dust, 3 pollen + animal dander, 1 pollen + animal dander+ mold, 1 house dust + animal dander, 1 pollen + house dust + animal dander + mold.

When the patients with pollen ( $n=28$ ), house dust ( $n=17$ ) and multiple type allergen ( $n=18$ ) sensitization were compared among themselves; there was no signifi-

cant difference between age, gender, disease duration, presence of angioedema, total IgE levels, autoantibody positivity, sedimentation, CRP and C3 levels, whereas there was a significant difference between C4 levels ( $p=0.026$ ). C4 levels were higher in the pollen group ( $33.56\pm 10.93$  mg/dl) than in the house dust group ( $30.17\pm 7.78$  mg/dl), and higher in the house dust group than in the multiple type allergen group ( $25.53\pm 5.55$  mg/dl). There was a significant difference between the pollen group and the multiple type allergen group ( $p=0.007$ ) (Table II).

There was more atopic disease history in the multiple type allergen group than the house dust group and pollen group. No significant difference was found between the groups (Table II). Antihistamine treatment response was better in the pollen group than the house dust group and multiple type allergen group. However, no significant difference was found between the groups (Table II).

**Table II:** Evaluation of clinical and laboratory features in patients with atopic CSU according to skin prick test allergen types

	<b>Pollen</b> n=28 (44.4%)	<b>House Dust</b> n=17 (27%)	<b>Multi type allergen</b> n=18 (28.6%)	<b>p-value</b>
Age, year, mean±SD	41.21±12.86	38.58±12.79	34.86±9.97	0.57
Female, n (%)	16 (57.1)	11 (64.7)	9 (50.0)	0.68
Disease duration, month, median (min-max)	29 (11-240)	36 (6-228)	24 (8-120)	0.57
Angioedema, n (%)	8 (28.6)	8 (47.1)	7 (38.9)	0.44
High total IgE (≥100 IU/mL), n (%)	20 (71.4)	10 (58.8)	12 (70.6)	0.65
Total IgE (IU/mL), median (min-max)	246 (14-1712)	134 (22-2926)	187 (14-917)	0.92
Sedimentation (mm/h), median (min-max)	18 (2-43)	11 (2-34)	8 (2-38)	0.48
CRP (mg/L), median (min-max)	2 (1-29)	2 (1-18)	3 (1-23)	0.79
C3 (mg/dl), mean±SD	140.26±16.15	132.23±18.81	132.2±22.15	0.29
C4 (mg/dl), mean±SD	33.56±10.93	30.17±7.78	25.53±5.55	<b>0.026</b>
History of atopic disease, n (%)	13 (46.4)	5 (29.4)	10 (55.6)	0.28
• AR	13 (46.4)	3 (17.6)	8 (44.4)	0.12
• Asthma	5 (17.9)	4 (23.5)	5 (27.8)	0.74
Antihistamine treatment response, n (%)	19 (67.9)	8 (47.1)	9 (50.0)	0.30

**Ig:** immunoglobulin, **CRP:** C-reactive protein, **C:** complement, **AR:** allergic rhinitis, **min:** minimum, **max:** maximum

Data are presented as mean ± SD or median (min-max). Statistical analyses were performed using Student's t-test or the Mann-Whitney U test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables.

## DISCUSSION

In our study, 89 patients (34.1%) were considered atopic. Female gender, thyroid autoantibody (TPO, Tg) positivity, and ANA positivity were significantly higher in the nonatopic group while total IgE levels, and the rate of high total IgE and C4 levels were higher in the atopic group. The higher incidence of female gender and autoantibody positivity in the non-atopic group suggests that autoimmunity may play a greater role in this group. Type I autoimmune response (autoallergic) and type IIb autoimmune response have been defined in the pathogenesis of CSU. In type I autoimmunity (autoallergic) response, autoallergens including IL-24, tissue factor, tissue transglutaminase 2, thyroglobulin, thyroid peroxidase, FcεR1 form complex with IgE and mast cell activation occurs via FcεR1 (4,10-14). Type IIb autoimmune response occurs via IgG produced against FcεR1 or FcεR1-bound IgE on the surface of mast cells or basophils (4,15-17). Both mechanisms involve cross-linking of FcεR1 and overlap has been observed in most patients with CSU (4,14,18,19). Recent studies have yielded results suggesting that the disease may be associated not only with endogenous antigens but also with exogenous antigens (2). Studies have shown that both a history of atopic disease and specific IgE positivity against various allergens, as shown by atopy

rates, are frequently observed in patients with CSU (2, 20). It is observed that the positivity of skin prick test or serum specific IgE in patients with CU varies between 17.2% and 95.83% and is higher compared to healthy controls. The sensitization detected in studies was mostly related to aeroallergens, and rarely related to food allergens. The most commonly detected aeroallergen sensitization is to house dust, followed by pollen (2,6-9,21-28). In a meta-analysis examining the risk of atopic disease in patients with chronic urticaria, the estimated prevalence in adult CU patients was 5% for AD, 14% for asthma, and 22% for allergic rhinoconjunctivitis (ARC) (29). However, studies are heterogeneous, and not all studies have confirmed atopy with specific IgE tests. In our study, 19.9% of patients with CSU had a history of atopic disease, 0.3% had AD, 12.6% had asthma, and 12.3% had AR. However, in our study, the rate of specific IgE-based atopy was 34.1% and half of the patients had high total IgE levels. These rates are too high to be coincidental and suggest that atopy may be associated with chronic urticaria. In our study, high total IgE (3.92 fold risk, 95% CI) and C4 elevation (2.41 fold risk, 95% CI) were found to be independent risk factors for atopy in regression analyses.

Although different types of allergens are mentioned in the studies, house dust sensitivity is particularly striking

(6-8,20-22,24,26,28). In a previous study we conducted with a group of patients with allergic rhinitis, we found that 66% of the patients had sensitivity to pollen, 10.8% to house dust, and 23.2% to both pollen and house dust (30). In this study, we found that 44.4% of the atopic CSU cases had sensitivity to pollen, 27% to house dust, and 28.6% to multiple type allergen. In our region, which has a climate and geography where pollen is intense and lasts for a long time, we observed that house dust sensitivity was higher in patients with CSU, unlike our patients with allergic rhinitis. Considering the persistence of symptoms in patients with chronic spontaneous urticaria and the year-round exposure to house dust, it can be thought that house dust may play a role in the pathogenesis of CSU in at least some of the patients. However, today, due to reasons such as climate change and global warming, the duration of exposure to pollen seems to have extended. In regions where pollen is dense and exposure almost all year round, as in our region, it can be thought that pollen may also affect the disease course.

The clinical significance of atopy in patients with chronic urticaria is not clear. Song et al. reported that the Urticaria Activity Score (UAS) and Dermatology Life Quality Index (DLQI) were higher in patients with CSU who were sensitive to house dust mites (26). Kulthanan et al. reported a clinical relationship between allergen sensitization and urticarial symptoms (22). Since our study was retrospective, the disease activity index could not be evaluated. However, patients who did not respond to antihistamines and were started on omalizumab may be considered to have a more active disease course. In our study, there was no difference in antihistamine treatment response between atopic and nonatopic groups. In our study, as expected with high total IgE and history of atopic disease, total IgE levels were higher in atopic patients compared to non-atopic patients. C4 levels were also higher in the atopic group. Interestingly, female gender, thyroid autoantibodies and ANA positivity were higher in the nonatopic group. Similarly, there was a female predominance in the non-atopic patient group in the Chen et al. study. In this study, disease duration of  $\geq 12$  months was higher in the non-atopic group (20). Ping et al. reported that allergen sensitization is higher in males (6). Park et al. have suggested that allergen sensitization is a risk factor for a longer disease duration in patients with chronic urticaria (7). In our study, disease durations did not differ between groups. In the study, ASST (autologous serum skin test) was found to be similar in both groups. Although the history of autoimmune disease was higher in the non-atopic group, no

significant difference was found (20). ASST was not applied in our study. We can interpret autoimmunity based on ANA and thyroid autoantibodies, which were higher in the non-atopic group. In the study, although the criteria of atopy were different, atopy was detected in 48.9% of patients, and angioedema, anaphylaxis and dermatographism were more common in atopic patients. They indicated that atopy could be a risk factor for angioedema and anaphylaxis (20). We did not observe any difference in the frequency of angioedema between the groups.

No correlation has been found between total IgE levels and antihistamine treatment response in patients with CSU (31,32). In our study, similar to other studies, we did not observe any difference in antihistamine response between atopic and nonatopic CSU patients (20). Even if atopy or autoimmunity were responsible for the etiopathogenesis, we thought that there was no difference in antihistamine response because the primary effector cells were mast cells.

When disease characteristics were compared according to allergen types, C4 levels differed ( $p=0.026$ ). This difference was due to the pollen sensitized group and the group with multiple sensitized group ( $p=0.007$ ). In our study, C4 levels were higher in the atopic patient group and C4 elevation was more pronounced in the pollen sensitised group. Plavsic et al. have shown a correlation between urticaria disease activity and C4 levels. They found that inflammation markers C-reactive protein and C4 are increased in patients with chronic spontaneous urticaria, suggesting that inflammation may play a role in the pathogenesis of CSU. The finding that elevated C4 levels are associated with disease activity in patients with chronic urticaria highlighted the possibility that elevated C4 levels may be a marker of disease activity, but further studies are needed to investigate this (33). Kasperska-Zajac et al. found that patients with moderate to severe symptoms had higher C3 and C4 concentrations than patients with mild CU and healthy individuals (34). In patients with active urticaria, the increase in C4 may be a result of increased hepatic synthesis in response to pro-inflammatory cytokines (33,35). Perhaps elevated C4 may be an indicator of the acute phase response. The finding of higher C4 levels in the atopic group in our study suggests that atopy may contribute to inflammation in chronic urticaria. The higher C4 levels detected in the pollen-sensitive group may indicate more inflammation, but further studies are also needed to investigate this.

The limitation of the study was the lack of urticaria activity scores. Since skin prick tests could not be performed in some patients, aeroallergen serum-specific IgE positivity was also accepted as atopy. However, as the serum aeroallergen-specific IgE subgroup distinction could not be made in these patients, only skin prick test results were used as a basis to determine disease characteristics according to allergen types.

In conclusion, total IgE levels, high total IgE rates, and history of atopic disease were higher in the atopic group while female gender, thyroid autoantibody positivity and ANA positivity were significantly higher in the nonatopic group. Due to the high prevalence of atopy, and despite the overlap, patients with chronic spontaneous urticaria can be classified as atopic and nonatopic (autoimmune), and this classification can also be effective in determining the step treatment method.

#### Conflict of Interest

No conflict of interest in this study.

#### Author Contributions

Concept: **Songul Cildag**, Design: **Songul Cildag**, **Gokhan Sargin**, Data collection or processing: **Songul Cildag**, Analysis or Interpretation: **Songul Cildag**, **Gokhan Sargin**, Literature search: **Songul Cildag**, **Gokhan Sargin**, Writing: **Songul Cildag**, **Gokhan Sargin**, Approval: **Songul Cildag**, **Gokhan Sargin**.

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