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Autoimmunity and Clinical Markers in Chronic Spontaneous Urticaria: A Retrospective Cohort Study

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ABSTRACT

BACKGROUND.

Chronic spontaneous urticaria (CSU) is a skin condition that results in itchy hives or welts on the skin. The underlying cause of CSU is not fully understood, but it is believed to be mainly associated with autoimmunity.

OBJECTIVES

In this retrospective study, we analyzed correlations between several clinical and biological markers and their associations with disease control, response to H1-antihistamines, autoimmunity (ANA, IgG-anti-TPO), and distribution of comorbidities.

METHODS

The study was conducted from September 2020 to December 2022 at the Center of Allergy and Immunology in Tbilisi, Georgia. 131 adults and adolescents (≥ 12 years old) with a diagnosis of CSU were included.

RESULTS

Among the 131 patients included in the study, 83% (n=109) were female, and 17% (n=22) were male. The average age was 33.71 years (range 12-76). Antinuclear antibodies (ANA antibodies) were found to be positive in 17% of patients, while 33% had IgG-anti_TPO antibodies. Comparison between the controlled (n=83) and the uncontrolled disease group (n=48) shows that there is no substantial difference in age, but there are significant differences in sex (more females in the controlled group), total IgE (lower in the uncontrolled group), and the presence of ANA and anti–thyroid peroxidase (anti-TPO) antibodies (both higher in the uncontrolled group). The p-values for sex, total IgE, ANA, and anti-TPO are 0.003, 0.007, 0.03, and 0.028, respectively.

CONCLUSIONS

The results suggest that autoimmunity may play a role in the development of CSU and that treatments targeting the underlying autoimmune response may be effective in managing the condition.

KEYWORDS

Autoimmunity, ANA antibodies; chronic spontaneous urticaria; IgG-anti-TPO antibodies; total IgE.

BACKGROUND

Chronic spontaneous urticaria (CSU) is a skin condition characterized by the presence of itchy hives or welts on the skin that appear and disappear spontaneously.[1] The exact cause of CSU is not fully understood, but it is believed to be associated with autoimmunity in many cases.

In the case of CSU, it is thought that the immune system mistakenly targets certain cells in the skin, resulting in characteristic hives and inflammation.[2] The evidence indicates that autoimmunity is present in up to 50% of CSU cases, and the presence of autoantibodies is associated with a more severe and prolonged course of the disease. Additionally. the presence of other autoimmune conditions, such as thyroid disease or rheumatoid arthritis, may increase the likelihood of developing CSU.[3]

Understanding the role of autoimmunity in CSU is important for the development of effective treatment strategies. In some cases, treatments that target the underlying autoimmune response, such as immunosuppressive medications or plasmapheresis, may be effective in managing the condition.[4] Autoimmune diseases, particularly autoimmune thyroiditis, and thyroid AAbs, seem more prevalent in patients with CSU.[5,6]

Several AAbs have been associated with CSU: IgG against thyroperoxidase (TPO) or thyroglobulin (Tg),[5,7] IgG against IgE or high-affinity IgE receptor (FceRI),8,9 and IgE directed against autoantigens, such as TPO or interleukin 24.[10,11] Furthermore, some patients with CSU react to the intradermal injection of their serum resulting in a positive autologous serum skin test (ASST).[12]

In this retrospective cohort of patients with CSU, we analyzed correlations between several clinical and biological markers and their associations with (i) disease activity, (ii)

response to H1-antihistamines, (iii) autoimmunity (ANA, IgG-anti-TPO), (iv) distribution of comorbidities.

METHODS

This retrospective study was conducted from September 2020 to December 2022 at the Center of Allergy and Immunology (Tbilisi, Georgia). Overall, 131 adults and adolescents (≥ 12 years old) with a diagnosis of CSU, confirmed by an allergologist according to the international Guideline,[4] were included. Only omalizumab-naïve patients with active CSU were selected. In the management of patients, only new-generation antihistamine drugs, H2 blockers, were used. An immunofluorescent technique with HEp-2 cell substrate was used for ANA testing (the results were reported as a titer). The cut-off value to define positive ANA was 1:80. IgG-anti-TPO test was considered positive if its level was > 34 kU/l. According to the urticaria control state, the patients were divided into two groups: controlled and uncontrolled. The UCT scale was used to assess the severity of the patient's disease. Patients were evaluated at the first and second visits, with an interval of 4 weeks between visits. UCT 0 to 12 points were assessed as uncontrolled, and 12 to 16 were controlled diseases.

Statistical analysis

Differences in continuous variables between test samples were analyzed using a t-test for independent samples and the Mann-Whitney U test, while the Chi-Square test was used to see differences in categorical variables. Normally distributed data are presented as mean ± SD, and nonnormally distributed data are expressed as a median. Data were analyzed by DATAtab: an online Statistics Calculator. Statistical significance was defined as $p < 0.05$.

RESULTS

Among the 131 patients included in this study with an average age of 33.71 years (12-76), 83% (n=109) were females, and 17% (n=22) were males. The results of the descriptive statistics show that the female group had lower values for the total IgE (median 87.35) than the male group (median 133.5). The Mann-Whitney U-Test showed that the difference between females and males concerning the dependent variable total IgE was not statistically significant (p=0.234). A statistically significant correlation was observed between the total IgE level and the control of urticaria. In particular, the total IgE level was lower in the uncontrolled group of patients (p=0.007, r=0.24). Table 1 represents the demographic, clinical, and laboratory characteristics of study patients.

Antinuclear antibodies (ANA antibodies) were determined in 97 patients, of which 83% (n=80) were negative, and 17% (n=17) were positive. Out of 80 negative tests, 72 were women, and 8 were men, and out of 17 positive results, 16 were women and 1 man (p=0.595). There was no statistically significant relationship between sex and ANA. Comparative analysis revealed a statistically significant correlation between ANA positivity and urticaria control (p=0.03). No statistically significant correlation was found between total IgE level and ANA positivity. A point-biserial correlation was run to determine the relationship between Total IgE and ANA. There was an insignificant negative correlation between Total IgE and ANA (p = 0.32). In the majority of ANA-positive patients, the pattern was nuclear speckled.

TABLE 1. Demographic, clinical, and laboratory characteristics of patients

	Number	*%*
Total Number of Patients	131	
Gender (Female/Male)	109/22	83/17
Age (years) (Mean ± SD)	33.71 ± 16.07	
Total IgE kU/l (median)	95.45 (min: 2.39, max: 4417)	
ANA (Positive/Negative)	17/80	17/83
IgG-anti-TPO (Positive/Negative)	40/81	33/67
Comorbidity (Yes/No)	62/69	47/53
UCT at Visit 1 (Uncontrolled/Controlled)	131/0	100/0
UCT at Visit 2 (Uncontrolled/Controlled)	48/83	36/64

Abbreviations: ANA: Antinuclear antibodies; IgE: Controlled: controlled disease, UCT score from 12 to 16; Immunoglobulin E; IgG-anti-TPO: immunoglobulin G subclass of anti-thyroid peroxidase; SD: standard deviation; UCT: urticaria control test; Uncontrolled: uncontrolled disease, UCT score from 0 to 12.

A thyroid autoimmunity assessment test (IgG-anti-TPO) was performed on 121 patients. 33% (n=40) of them are positive, while 67% (n=81) are negative. Out of 81 negative tests, 66 are women, and 15 are men, and out of 40 positive results, 35 are women, and 5 are men (p=0.402). There was no statistically significant relationship between sex and IgG-anti-TPO. Comparative analysis revealed a statistically significant correlation between thyroid autoimmunity and urticaria control (p= 0.028).

The obtained data revealed a positive correlation between thyroid autoimmunity and the positivity of antinuclear antibodies. A Chi^2 test was performed between IgG-anti-TPO and ANA. At least one of the expected cell frequencies was less than 5. Therefore, the assumptions for the Chi^2 test were not met. There was a statistically significant relationship between IgG-anti-TPO and ANA, $\chi^2(1)=7.01$, p=0.008.

Among the patients participating in the study comorbidity was detected in 47% (n=62) persons. The distribution of concomitant diseases is given in Figure 1.

At the first visit, 100% of patients had UCT < 12, i.e., uncontrolled. At visit two, 64% (n=83) of the disease was controlled, and 36% (n=48) were uncontrolled. 63 of the controlled patients are women, 20 men, and 46 women and 2 men of the uncontrolled patients. There was a statistically significant relationship between sex and visit two UCT scores, $\chi^2(1)=8.64$, p=0.003.

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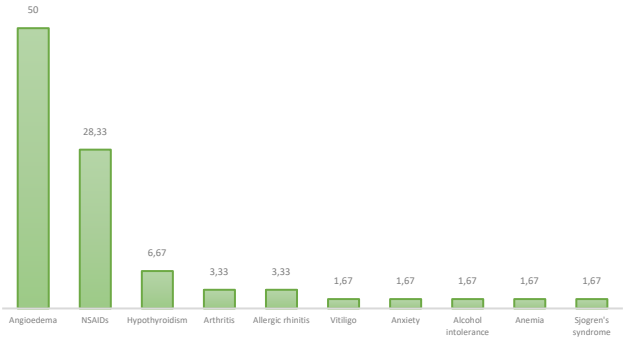
FIGURE 1. The distribution of comorbid diseases (%)



Statistically significant data obtained from the results of the research are summarized in Table 2.

TABLE 2. Comparison between controlled and uncontrolled groups

	Controlled n=83	*Uncontrolled n=48*	*P value*
Age	32.92	35.08	0.678[a]
Female sex	63	46	**0.003**[b]
Total IgE (kU/l)[1]	120	54.6	**0.007**[c]
ANA-positive	35%	65%	**0.03**[b]
Anti-TPO-positive	25%	45%	**0.028**[b]

Abbreviations: ANA: antinuclear antibodies; anti-TPO: anti–thyroid peroxidase immunoglobulin G; IgE: immunoglobulin E.
[1] Total IgE median.
[a] t-test for parametric variables
[b] Chi-square test
[c] Mann-Whitney U test

DISCUSSION

The findings of this study suggest that there may be a relationship between autoimmune markers and chronic spontaneous urticaria. The correlation between ANA positivity and urticaria control suggests that the presence of ANA antibodies may be associated with a more severe form of the disease. Similarly, the correlation between thyroid autoimmunity and urticaria control suggests that thyroid autoimmunity may also play a role in the severity of chronic spontaneous urticaria. ANAs are a group of autoantibodies directed against nucleus antigens and are found in many patients with autoimmune diseases. These autoimmunity markers are positive in patients with CU by approximately 15–29%.[13]

Our study showed that ANA positivity is 17%. The detection of ANAs in serum has been carried out for several years to screen for autoimmune diseases, but this analysis lacks some degree of subjectivity. While it may be important to acknowledge the presence of these autoimmune markers to understand the CU mechanism, its role is not fully explained, nor are its research criteria fully defined. Margen et al. published a study aimed at identifying clinical and laboratory attributes of patients with positive ANAs and CU.[13] One of the conclusions of the study was that this subgroup of patients (with positive ANAs) was characterized by greater refractoriness to treatment with standard licensed doses of antihistamines, even though most patients do not have associated autoimmune diseases.[14]

Our study revealed a reliable correlation between ANA positivity and uncontrolled disease. It has been reported that the prevalence of anti-TPO in patients with chronic urticaria is higher than in the general population.[15] The prevalence of anti-TPO in the general population is 3%–6%, while the incidence in patients with chronic urticaria is reported to be 5%–34%.[13, 15,16, 17] In our study, 4 patients had hypothyroidism, and all others only had positive anti-TPO antibodies. The rate of positivity in our population was 33%.

According to the data of our study, a statistically significant correlation was found between thyroid autoimmunity and ANA antibody positivity. This once again shows in favor of the autoimmune pathogenesis of chronic urticaria. Up to 41% of autoimmune CSU patients exhibit significantly lower total IgE levels (< 40 IU/mL) and higher anti-TPO IgG levels. Elevated anti-TPO IgG and low total IgE have been shown as a predictor for low response to antihistamines and a useful diagnostic marker for autoimmune CSU.[18,19] Similar to what has been reported in the literature, our findings show a relationship between urticaria control and total IgE levels.

It is worth noting that the study did not find a statistically significant relationship between sex and ANA or IgG-anti-TPO positivity, indicating that these autoimmune markers may be equally relevant for both men and women with chronic spontaneous urticaria. However, the study did find a significant relationship between sex and urticaria control, with a higher proportion of women achieving control at the second visit. This may indicate that there are sex-specific differences in the response to treatment for chronic spontaneous urticaria.

The results of this study have important clinical implications, as they suggest that the presence of autoimmune markers may be useful in predicting the severity of chronic spontaneous urticaria. Further studies are needed to confirm these findings and to explore the underlying mechanisms linking autoimmune markers and chronic spontaneous urticaria. Additionally, studies should investigate potential sex-specific differences in the pathophysiology and treatment response of chronic spontaneous urticaria.

While the study has some limitations, such as the small sample size and lack of a control group, it provides important insights into the potential underlying mechanisms of refractory urticaria and the need for further research in this area.

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CONCLUSION

In this retrospective cohort study, we found a high prevalence of autoimmunity in patients with chronic CSU, as evidenced by the presence of ANA and anti-TPO antibodies. These findings support the growing body of evidence that autoimmunity plays a significant role in the pathogenesis of CSU. Further studies are needed to investigate the relationship between autoimmunity and disease activity, as well as the potential role of immunosuppressive therapies in the management of CSU.

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