

# ASSOCIATION OF AUTOIMMUNE STATUS WITH ASST, AUTOIMMUNE AND ATOPIC DISEASES IN CSU PATIENTS

Vesna Trajkova<sup>1\*</sup>, Nevenka Velickova<sup>2</sup>

<sup>1</sup>City General Hospital "8mi Septemvri", Skopje, Republic of North Macedonia, e-mail: [vesna.dojcinovska@gmail.com](mailto:vesna.dojcinovska@gmail.com)

<sup>2</sup>Faculty of medical sciences, University "Goce Delcev" - Stip, Republic of North Macedonia,  
e-mail: [nevenka.velickova@ugd.edu.mk](mailto:nevenka.velickova@ugd.edu.mk)



**Abstract:** Chronic spontaneous urticaria (CSU) is a mast cell-driven skin disease characterized by the recurrence of transient wheals, angioedema, or both for more than 6 weeks. Autoimmunity is thought to be one of the most frequent causes of CSU. CSU represents an important burden that compromises patient's quality of life, interferes with routine daily activities. Aim of the study: The aim of this study is to make an association of autologous skin serum test (ASST), autoimmune diseases and atopic diseases with the autoimmune status in patients with HSU. Materials and methods: This study assessed 230 patients with CSU. The study is prospective, proceeding at the Department of Dermatology at City General Hospital "8mi Septemvri", Skopje, in the period from January - November 2021. The study and the data collection were conducted with the approval of the institutional and ethical committee. Inform consent was obtained from all patients. Patients were divided in two groups according to their autoimmune status: patients with positive and patients with negative autoimmune status. Autoimmunity was defined in the case of a personal history of autoimmune disease or in the presence of at least one type of autoimmune antibodies (AABs) (included anti-TPO, anti-nuclear antibodies (ANA) and rheumatoid factor (RF)). ASST was performed on untreated patients by the intradermal injection of 50 µL of the patient's own serum into the volar part of the forearm. Anamnestic data on the course of the disease, accompanying autoimmune diseases and allergic diseases were taken. Results: Positive autoimmune status was confirmed in 40.28% of patients with HSU. Patients with a positive autoimmune status significantly more often than patients without an autoimmune status had a certain autoimmune disease (75.17% vs 10.59%): Hashimoto Tireoiditis 39.31% vs 10.59%, Vitiligo 13.79%, Arthritis Rheumatica 9.66%, Morbus Crohn 5.52%, Hashimoto Tireoiditis + Vitiligo 6.9%. Patients had a personal history of atopy (67.59% vs 55.29%), asthma (61.38% vs 44.71%), personal history for allergic rhinitis (57.24% vs 49.41%), positive ASST (86.9% vs 16.47%). To conclude, in this study, we obtained a high incidence of association of ASST, autoimmune diseases and atopic diseases with positive autoimmune status in CSU patients, thus providing additional evidence in the association of HSU with autoimmunity.

Keywords: *Chronic spontaneous urticaria; autoimmunity; autologous skin serum test, autoimmune diseases, atopic diseases*

Field: *Medical sciences and Health*

## INTRODUCTION

Chronic spontaneous (idiopathic) urticaria (CSU), is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks [1]. CSU is a benign condition and is directly related to mast cell degranulation, which releases a number of cellular mediators that activate the disease [1]. Epidemiologically, the prevalence of CSU varies 0.23% - 1.8% worldwide [2]. CSU represents an important burden that compromises patient's quality of life, interferes with routine daily activities [2]. Etiological trigger by definition is not known, but possible causes are: autoimmune mediated antibodies against IgE receptors with high affinity, IgE autoantibodies to antigens, acute or chronic infections [1]. Pathophysiological degranulation of mast cells leads to the release of immune mediators: histamine (which binds to the H<sub>1</sub>-receptor of endothelial cells and sensory nerves), prostaglandins, leukoreins, cytokines, chemokines [1]. There is a strong association of HSU with atopic diseases, allergic rhinitis, atopic dermatitis and asthma [3]. Numerous autoimmune conditions have a high prevalence in CSU patients: thyroid diseases, celiac disease, Sjogren's syndrome, systemic lupus, rheumatoid arthritis and type 1 diabetes mellitus [4]. The autologous skin serum test (ASST) is performed in order to examine autoimmunity and detect circulating autoantibodies in patients with CSU [2]. The above mentioned factors, alone or combined are often used to classify patients as autoimmune and non- autoimmune CSU. [3]

\*Corresponding author: [vesna.dojcinovska@gmail.com](mailto:vesna.dojcinovska@gmail.com)



## AIM OF THE STUDY

The aim of this study is to make an association of autoimmune diseases, atopic diseases and ASST with the autoimmune status in patients with HSU, and thus to indicate the association of HSU with autoimmunity and atopic diseases.

## MATERIALS AND METHODS

This prospective study was conducted from January 2022- November 2022 in the department of Dermatology in City General Hospital "8mi Septemvri", Skopje, North Macedonia. The study assessed 230 patients with CSU. Patients 18-70 years old with a diagnosis of CSU, confirmed by a dermatologist according to the international Guideline 2013 [ 5]., were included.

Patients were divided in two groups according to their autoimmune status: patients with positive and patients with negative autoimmune status. Autoimmunity was defined in the case of a personal history of autoimmune disease or in the presence of at least one type of autoimmune antibodies (AAbs) (included anti- TPO, anti-nuclear antibodies (ANA) and rheumatoid factor (RF)).

ASST was performed by the intradermal injection of 50  $\mu$ L of the patient's own serum into the volar part of the forearm. Positive test: appearance of a red wheal with a diameter of 1.5 mm or greater than the wheal produced by the injection of normal saline solution within 20 minutes. Positive control: Prick tests with histamine. Negative control: Intradermal injection of normal saline solution [3, 5].

Medical history, including history of personal or familial atopy (asthma, atopic dermatitis and allergic rhinitis) and autoimmune diseases, as well as previous and current treatments for CSU were recorded.

The study and the data collection were conducted with the approval of the institutional and ethical committee. Inform consent was obtained from all patients.

Statistical processing: The statistical analysis of the research data was carried out in the statistical program SPSS 23.0. Kolmogorov-Smirnov test and ShapiroWilk's test were used to test the normality of the distribution of the data. The obtained data are presented tabularly and graphically.

## RESULTS

In the studied group of patients, positive autoimmune status was confirmed in 145 (40.28%) patients with CSU (Figure 1).

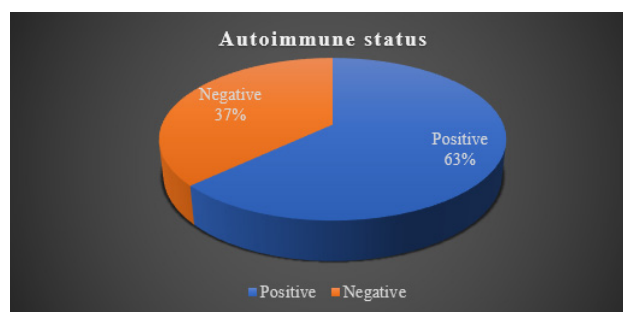


Figure 1. Autoimmune status in patients with CSU

Table 1 shows that 67.59% and 55.29% of patients had a personal history of atopy, respectively, with positive and negative autoimmune status.

Patients with a positive autoimmune status significantly more often than patients with a negative autoimmune status had a certain autoimmune disease (75.17% vs 10.59%;  $p < 0.0001$ ): presence of Hashimoto Thyroiditis 39.31% in patients with a positive autoimmune status, 10.59% in patients with a negative autoimmune status, presence of Vitiligo 13.79% in patients with a positive autoimmune status and no presence in patients with a negative autoimmune status, presence of Arthritis Rheumatica 9.66% in patients with positive autoimmune status and no presence in patients with negative autoimmune status, presence of Morbus Crohn 5.52% in patients with positive autoimmune status and no presence in patients with negative autoimmune status, presence of Hashimoto Thyroiditis + Vitiligo 6.9% in patients with

positive autoimmune status and absent in patients with negative autoimmune status (Table 1, Figure 2).

Patients with autoimmune status significantly more often than patients with negative autoimmune status had asthma (61.38% vs 44.71%;  $p=0.014$ ) (table 1, Figure 3).

Personal history of allergic rhinitis was present in 57.24% of patients with positive and 49.41% of patients with negative autoimmune status (Table 1).

Table 1. Association of autoimmune status with allergic and atopic diseases

|   | Autoimmune status |                   |                   | p-level                  |
|---|-------------------|-------------------|-------------------|--------------------------|
|   | n                 | Positive<br>n (%) | Negative<br>n (%) |                          |
| <b>Personal history of atopy</b>                          |                   |                   |                   |                          |
| Present   | 145               | 98 (67.59)        | 47 (55.29)        | $X^2=3.5$ $p=0.062$      |
| Not present   | 85                | 47 (32.41)        | 38 (44.71)        |                          |
| <b>Personal history of concomitant autoimmune disease</b> |                   |                   |                   |                          |
| Not present   | 112               | 36 (24.83)        | 76 (89.41)        | $X^2=89.5$ * $p=0.00000$ |
| Present   | 118               | 109 (75.17)       | 9 (10.59)         |                          |
| Hashimoto Tireoiditis                                     | 66                | 57 (39.31)        | 9 (10.59)         |                          |
| Vitiligo  | 20                | 20 (13.79)        | 0                 |                          |
| Arthritis Rheumatica                                      | 14                | 14 (9.66)         | 0                 |                          |
| Morbus Crohn  | 8                 | 8 (5.52)          | 0                 |                          |
| Hashimoto Tireoiditis + Vitiligo                          | 10                | 10 (6.9)          | 0                 |                          |
| <b>Personal history of asthma</b>                         |                   |                   |                   |                          |
| Present   | 127               | 89 (61.38)        | 38 (44.71)        | $X^2=6.02$ * $p=0.014$   |
| Not present   | 103               | 56 (38.62)        | 47 (55.29)        |                          |
| <b>Personal history of allergic rhinitis</b>              |                   |                   |                   |                          |
| Present   | 125               | 83 (57.24)        | 42 (49.41)        | $X^2=1.32$ $p=0.25$      |
| Not present   | 105               | 62 (42.76)        | 43 (50.59)        |                          |

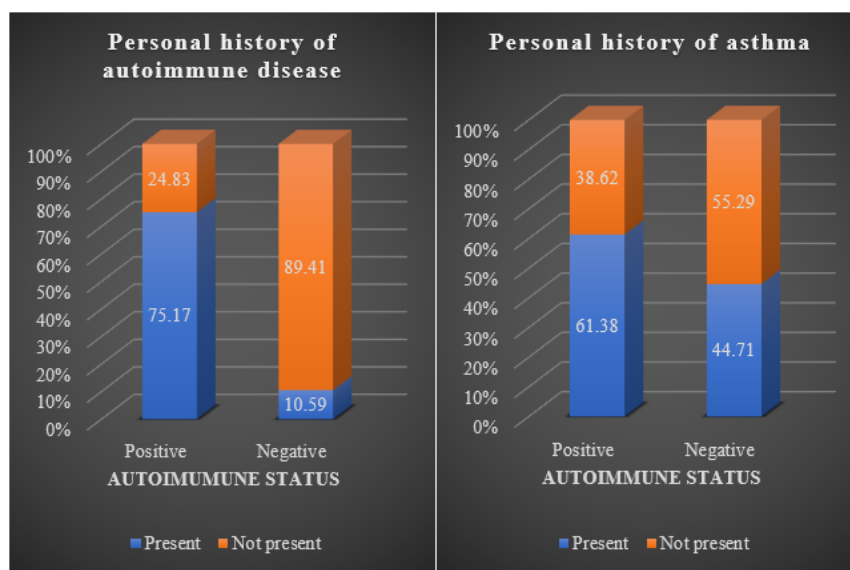


Figure 2

Figure 3

Figure 2. Association of autoimmune disease with personal autoimmune disease

Figure 3. Association of autoimmune disease with personal history of asthma

A positive ASST test was detected in 86.9% of patients with the presence of autoimmunity and in 16.47% of patients without autoimmunity. For  $p<0.0.0001$ , a statistically significant difference was confirmed in the distribution of patients with a positive and negative ASST test, depending on the immune status; A positive ASST test was significantly more often confirmed in patients with a positive autoimmune status (table 2, figure 4).

Table 2. Association of autoimmune status with ASST

|             | Autoimmune status |                   |                   | p-level                   |
|-------------|-------------------|-------------------|-------------------|---------------------------|
|             | n                 | Positive<br>n (%) | Negative<br>n (%) |                           |
| <b>ASST</b> |                   |                   |                   |                           |
| Positive    | 140               | 126 (86.9)        | 14 (16.47)        | $X^2=111.6$ * $p=0.00000$ |
| Negative    | 90                | 19 (13.1)         | 71 (83.53)        |                           |

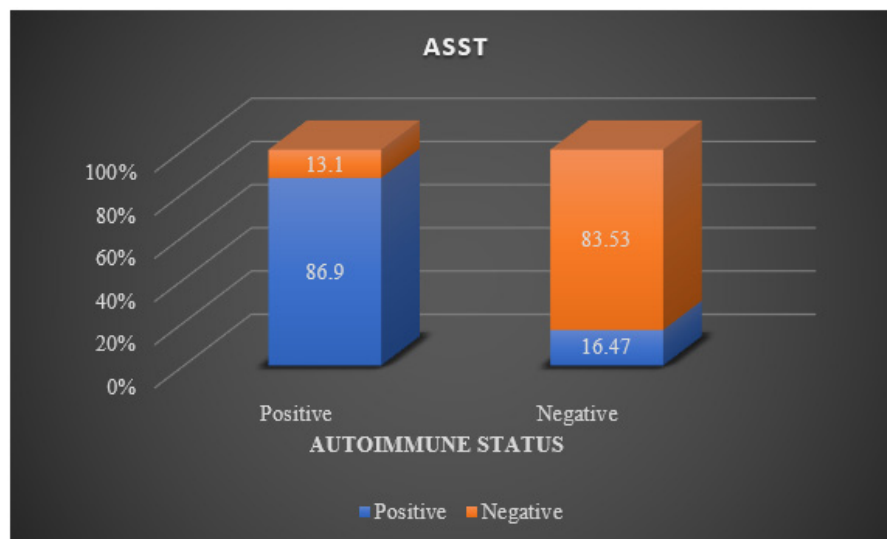


Figure 4. Association of autoimmune status with ASST

## DISCUSSION

Since nearly 30 years, several lines of evidence argue for an auto-immune basis of CSU, or at least in a subgroup of them, distinguishing autoimmune from non-autoimmune CSU, and the same is still a subject of debate [5,6,7]. We found a relatively high incidence of patients with HSU and a positive ASST and a strong association with positive autoimmune status. In a sentinel study conducted by Grattan et al., 12 patients with chronic urticaria were subjected to intradermal autologous serum injection [11]. Though theoretically performed by Grattan et al., the autoimmune etiology of CSU was further supported by formal development of the autologous serum skin test (ASST), an in vivo assay of mast cell activation that is induced by intradermal injection of a patient's serum [11]. We found a relatively high incidence of autoimmune disorders and atopic disease in patients with CSU. Study conducted by Bracken SJ et al. [8] confirms that patients with HSU have a higher incidence of rheumatoid arthritis, Sjögren's syndrome, Type 1 diabetes and systemic lupus than patients without HSU. In a recent large study of 12,778 CU patients by Cofino-Cohen et al. [9] it was found that 9.8% of patients had hypothyroidism, and the rheumatoid factor (RF), Diabetes mellitus I., Sjogren's syndrome, Celiac disease and SLE significantly worsened in patients with HSU than in patients in the control group. In the same study [9] anti-thyroid antibodies were significantly more common in CU patients than controls. In this study in patients with HSU we found a strong association with a personal history of atopy (asthma, atopic dermatitis or allergic rhinitis). In a study done by Chiu HYat all. [10] patients with HSU were associated with allergic rhinitis, atopic dermatitis, asthma, autoimmune thyroid disease, rheumatoid arthritis positive ASST test. Our study confirmed the association of autoimmune status with ASST, autoimmune and atopic diseases in patients with HSU.

## CONCLUSIONS

- A) In patients with HSU we found a strong association with a personal history of atopy (asthma, atopic dermatitis or allergic rhinitis).
- B) In patients with HSU, we found a positive correlation with patients in whom the presence of an autoimmune status has been confirmed.
- C) In patients with HSU and a positive ASST we found a strong association with positive autoimmune status.

## REFERENCES

- Dabija D, Tadi P. (August 10, 2020 ). Chronic Urticaria. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing;
- Wertenteil S, Strunk A, Garg A.( 2019 Jul) Prevalence estimates for chronic urticaria in the UnitedStates: A sex- andage-adjusted population analysis. *J. Am. Acad. Dermatol.*;81(1):152-156
- Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, GrattanCEH. (2009) EAACI/GA2LEN taskforce consensus report: the autologous serum skin test in urticaria. *Allergy*.;64(9):1256-68.
- Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. (n.d). Chronic urticaria and autoimmunity: associations foundin a large population study. *J Allergy Clin*
- Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, C EHG, et al. (2019). Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST Study. *Allergy*
- Kolkhir P., Altrichter S., Hawro T., Maurer M. (2018). C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. *Allergy* .;73(4):940–948. doi: 10.1111/all.13352.
- L. deMontjoye, A-S. Darrigade, A. Giménez-Arnau, A. Herman, L. Dumoutier , M.Baeck . (2020 Jan 20) Correlations between disease activity, autoimmunity and biological parameters in patients with chronic spontaneous urticaria. *Eur Ann Allergy Clin Immunol* doi: 10.23822/EurAnnACI.1764-1489.132.
- Bracken SJ, Abraham S, MacLeod AS. (2019 Mar 29). Autoimmune Theories of Chronic Spontaneous Urticaria. *FrontImmunol*. ;10:627. doi:10.3389/fimmu.2019.00627
- Confino-Cohen R., Chodick G., Shalev V., Leshno M., Kimhi O., Goldberg A. ( 2012). Chronic urticaria and autoimmunity: associations foundin a large population study. *The Journal of Allergy and Clinical Immunology*.;129(5):1307–1313. doi: 10.1016/j.jaci.2012.01.043.
- Chiu HY, Muo CH, Sung FC. (2018 Jul Apr 16) Associations of chronic urticaria with atopic and autoimmune comorbidities: a nationwide population-based study. *Int J Dermatol* .;57(7):822-829. doi: 10.1111/ijd.14000. Apr 16. PMID: 29663342.
- Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. (1986) A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. *Br J Dermatol*. 114:583–590. doi: 10.1111/j.1365-2133.1986.tb04065.x

