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Original scientific paper

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- 23 ИНСУЛИН-ЛАЈК ГРОУТ ФАКТОР-1 И ВАСКУЛАРНО ЕНДОТЕЛИЈАЛЕН ГРОУТ ФАКТОР – РАНИ ПРЕДИКТИВНИ БИОМАРКЕРИ ЗА РЕТИНОПАТИЈА НА ПРЕМАТУРИТЕТ**
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Professional paper

- 32 ASST AND AUTOIMMUNITY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA**
Trajkova Vesna¹, Velichkova Nevenka², Breshkovska Hristina³
- 39 LIFE THREATENING UROLOGY CONDITIONS AS COMPLICATIONS OF SARS COV2 INFECTION – SYMPTOMS, DIAGNOSE, CONSERVATIVE, OPERATIVE AND POST-OPERATIVE TREATMENT**
Ivchev J^{1,2}, Gjorevski A^{2,3}
- 47 INDEX OF THE OSTEOPOROTIC RISK IN THE EVALUATION OF THE DENOSUMAB TREATMENT**
Slavica Shubeska Stratrova^{1,5}, Snezana Markovik Temelkova^{1,5}, Irfan Ahmeti^{1,5}, Jasmina Meceska Jovcevska², Dejan Spasovski^{3,5}
- 54 HEARING RECOVERY IN PATIENTS WITH IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS**
Lidija Ristovska¹, Zora Jachova²
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Петрушевска Андријана, Голубовиќ Милена, Ѓошевска Даштевска Емилија, Нивичка Каева Јана
- 65 DHURIMI I GJAKUT NË KOMUNËN E TETOVËS NË PERIUdhËN 2018 - 2021**
Ekrem Ismani¹, Sani Bajrami², Mazllum Belegu²
- 70 IMPLEMENTATION OF SHEAR WAVE ELASTOGRAPHY AS A NEW METHOD IN THE CLINIC OF GASTROENTEROHEPATOLOGY – SKOPJE**
Arzana Hasani Jusufi, Meri Trajkovska, Atip Ramadani, Arta Bina, Xhem Adem, Georgi Janevski.
- 77 MATERNAL PLASMA BIOMARKERS (ANTITHROMBIN 3, PLASMOINOGEN ACTIVATOR INHIBITOR 1, SOLUBLE TIE 2, VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR2) AS INDICATORS FOR PLACENTA ACCRETA SPECTRUM (PAS) IN THE THIRD TRIMESTER OF PREGNANCY**
Iva Malahova Gjoreska¹, Vesna Antovska¹, Goran Kochoski¹, Katerina Nikoloska¹, Josif Gjoreski¹

Review

- 81 МЕХАНИЧКИ ПОВРЕДИ НА ОЧИТЕ – МОЖНОСТИ ЗА НИВНА ПРЕВЕНЦИЈА И РЕХАБИЛИТАЦИЈА**
Ѓошевска Даштевска Емилија, Петрушевска Андријана, Голубовиќ Милена
- 87 EVALUIMI DHE MENAXHIMI I DHIMBYES SKROTALE**
Ilibert Ademi¹, Majlinda Ademi²
- 92 МОЖНИ КОМПЛИКАЦИИ ОД ФАКОЕМУЛЗИФИКАЦИОНА ХИРУРГИЈА НА КАТАРАКТА**
Велковска Б¹, Трпевска Шекеринов Н^{1,2}, Петрушевска А¹, Нивичка Каева Ј^{1,2}, Шекеринов Д³
- 100 EMBRYOLOGY, MORPHOLOGY, CLASSIFICATION AND SURGERY OF SYNDACTYLY**
Ermira Hamzai¹, Djordje Dzokic², Elizabeta Mircevskaja Zogovska²
- 106 SOME CONSIDERATIONS ABOUT POSTOPERATIVE NAUSEA AND VOMITING.**
Anna Mandi¹, Estela Muho¹, Majlinda Naço^{1, 2}, Haxhire Gani¹, Agron Dogjani³

Case report

- 111 ХИРУРШКИ ТРЕТМАН НА DIGITUS QUINTUS VARUS BILATERALIS**
Андријана Ѓорѓеска¹, Ѓорѓе Џокиќ¹, Томислав Јованоски¹, Маргарита Пенева¹, Христина Брешковска
- 119 LARGE OVARIAN CYST PRESENTING AS WEIGHT GAIN IN AN ADOLESCENT GIRL: A CASE REPORT**
Milica Pashoska¹, Elizabeta Stojovska Jovanovska², Zlatica Jovanovska², Marta Kamcheva², Marija Dukovska²
- 123 PERIRENAL URINOMA IN A YOUNG WOMAN AFTER CHILDBIRTH.**
Eva Shagla¹, Liri Cuko², Arlinda Hysenj¹, Ariola Fida¹, Agron Dogjani²
- 126 БИЛАТЕРАЛНО ЗГОЛЕМУВАЊЕ НА СУБМАНДИБУЛАРНИТЕ И ПАРОТИДНИ ЖЛЕЗДИ, ИНИЦИЈАЛЕН СИМПТОМ НА АКУТНА МИЕЛОИДНА ЛЕУКЕМИЈА**
Поповски В¹, Бранко А²
- 134 BROWN СИНДРОМ КАКО ПОСЛЕДИЦА НА РОДИЛНА ТРАУМА ВО ПРЕДЕЛ НА ДЕСНА ОРБИТА**
Беким Татеш¹, Сузана Кленкоски¹, Стефан Пандилов¹
- 139 CASES OF GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH COVID-19**
Teuta Dalipi¹, Ivan Barbov¹, Frosina Stojkovska¹, Jasmina Mitrevska Velkov¹, Marija Babunovska¹
- 143 POST-COVID-19 POLYRADICULONEURITIS WITH SEVERE RESPIRATORY INSUFFICIENTION. A CASE REPORT.**
Vanja Trajkovska^{1,2}, Biljana Andonovska^{1,2}, Maja Mojsova Mijovska¹, Saso Popovski¹, Amela Mumunovik¹
- 147 POST COVID-19 AUTOIMMUNE THYROID DISEASE IN 21 YEAR OLD MAN**
Daniela Misoska Pendova



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ASST AND AUTOIMMUNITY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA

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ABSTRACT

Objective: To invest possible association between HSU and: i) ASST ii) autoimmune diseases, iii) autoimmune serology, iv) atopy and dermatographism.

Methods: This is a perspective study. Patients with CSU (chronic spontaneous urticaria) were studied. UAS7 was applied to all of them. ASST and the following blood analyses were performed: anti-TPO, anti-nuclear antibodies (ANA) and rheumatoid factor (RF).

Results: We analyzed 48 patients with CSU; most of them were women, angioedema was associated with CSU in more than half of the patients, ASST was positive in more than one third of the patients and almost the same number of patients had positive autoimmune status. Almost half of the patients had a personal history of atopy and presence of dermatographism.

Conclusions: This study brings additional evidences of interest in patients with CSU as they could be associated to ASST and autoimmunity.

Keywords: Chronic spontaneous urticaria, ASST, autoimmunity

INTRODUCTION

Chronic spontaneous (idiopathic) urticaria (CSU), defined as the occurrence of wheals, angioedema, or both for more than 6 weeks, affects 1-2% of the population (1). Females are affected at least twice as often as males, and most patients are over 20 years of age (1). CSU represents an important burden that compromises patient's quality of life, interferes with routine daily activities (2). Several potential biomarkers for urticaria have been proposed, but only 5 of them have shown good clinical correlation: (3,4,5) Total serum IgE levels, C-reactive protein (CRP), Autologous serum skin test (ASST), Anti-thyroid peroxidase autoantibodies (IgG anti-TPO). Autoimmunity (ie, autoimmune mechanisms of skin mast cell activation) is held to be a frequent underlying cause of CSU (6). CSU is associated with autoimmunity

in 30-45% of the cases, sharing some immunological mechanisms with other autoimmune diseases, and is associated with autoimmune thyroid disease (ATD) in about 4.3% -57.4% patients (9). It is determined that patients with CSU have higher levels of anti-thyroid peroxidase (anti-TPO) antibodies, antinuclear antibodies (ANA), antithyroglobulin (i.e., antimicrosomal) antibodies, rheumatoid factor, anti-transglutaminase IgA antibodies, and anti-parietal cell antibodies with anti-dsDNA, and anti-cardiolipin antibodies trending toward significance (7). Autoimmune chronic spontaneous urticaria (CSU) is due to mast cell (MC)-activating autoantibodies, which are screened for by the autologous serum skin test (ASST) and basophil tests (BTs). (8). The above-mentioned factors, alone or combined are often used to classify patients as autoimmune and non- autoimmune CSU.

MATERIALS AND METHODS

This prospective study was conducted from January 2021- November 2021 in the department of Dermatology in City General Hospital “8mi Septemvri”, Skopje, North Macedonia. The study and the data collection were conducted with the approval of the institutional and ethical committee. Informed consent was obtained from all patients.

Patient selection and clinical data collection

Forty-eight adults and adolescents, 15-70 years of age, with a diagnosis of CSU, confirmed by a dermatologist according to the international Guideline 2013 (10), were included.

Inclusion criteria: Patients with active CSU.

Exclusion criteria: Patients with pure chronic inducible urticaria or bradykinin-mediated angioedema.

Also the 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 Weekly Urticaria Activity Score (UAS7) was used to assess disease activity (10). Patients were asked to record their symptoms for seven consecutive days prior to day of inclusion. Patients were classified as follows: severe CSU (UAS7 = 28-42), moderate CSU (UAS7 = 16-27), mild CSU (UAS7 = 7-15), well-controlled CSU (UAS7 = 1-6) and itch-and wheals- free (UAS7 = 0) (11).

Disease duration was defined as the time from the first onset of symptoms to day of inclusion. Recurring episodes of CSU, defined as recurrence of symptoms after at least 6 months of spontaneous remission, were also recorded.

For ASST and blood analyses, patients were considered as untreated, if they had stopped H1-antihistamines for at least 48 hours(12), anti-leukotrienes and H2-antihistamines for at least 7 days, and corticosteroids or cyclosporine

Autoimmunity

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)).

No autoimmunity was defined as the absence of autoimmune disease and AAbs.

Autologous skin serum test

ASST was performed on 48 untreated patients by the intradermal injection of 50 µL of the patient’s own serum into the volar part of the forearm (12).

Positive control: Prick tests with histamine

Negative control: Intradermal injection of normal saline solution.

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.

Patients were classified as having a positive or a negative ASST.

Biological tests

Blood analyses include the following autoimmune antibodies (AAbs): Anti-TPO, ANA and RF

Autoimmune Titers were considered positive if: Anti-TPO > 60 (0-60) U/ml, ANA > 1:160, and RF >15.9 (0-15.9)

Statistical analyses

Data for categorical variables are expressed as frequencies followed by the number of patients positive for this parameter in brackets over number of patients studied, and for continuous variables as mean ± standard deviation (SD) with minimum and maximum values in brackets.

RESULTS

Clinical data: This study included 48 patients with CSU, 34 of them were women (70,8%), and 14 of them were men (29.2%) (table 1,figure1), mean age in this study was 45.1 years (table 1) and mean duration of CSU in studied patients was 7.5 years (table 1).

Associations with angioedema: In this study angioedema was associated with wheals in 31 patients (64,5%) (table 1, figure 2).

Disease activity: Concerning disease activity based on UAS7 21/48patients (43.7%) had severe disease, 7/48patients (14.5 %) had moderate disease, 15/48 patients (31.2 %) had mild disease, 2/48 patients (4.1%) had well-controlled disease and 3/48 patients (6.5%) were itch-and wheals-free. (table 3, figure 3).

Associations with ASST: ASST was performed on 48 patients and 20of them (41.6%) were positive, and in 28 (58.4%) it was negative. (table 1,figure 4)

Associations with autoimmune disease: Considering the autoimmune status 17/48 patients (35,4%) had clinical history and/or serological markers of autoimmunity, and were considered as having a positive autoimmune status. (table 1, figure 5)

Personal history of autoimmune diseases was present in 13/48 patients (27%), familial history of autoimmune disease was found in 9/48 (18,7%) of cases(table 1, figure 6). In patients with personal history of autoimmune diseases Thyroiditis was found in 9/13 (69,2%), and Vitiligo was found in 4/13 (30,8 %)of the cases. (table 1, figure 7)

Associations withautoimmune serology: Considering autoimmune serology, anti-TPO was present in 10/48 (20,8 %) (table 2 , figure 8), ANA was present in 5/48 (10,4 %)(table 2, figure 9) and RF was present in 2/48 (4.1 %) (table 2, figure 10).

Associations withatopy and dermatographism: Almost half of the patients 27/48 (56,3 %)had a personal history of atopy and 14/48 (29,1%) of the patients had familial history of atopy (based on anamnesis) (table1, figure 11).Presence of dermatographism was confirmed in25/48 (52%) of the patients. (table 1, figure 12).

Tables

	N studied	Numbers (%) or mean ± SD (min-max)
Sex (female)	48	34 (70,8%)
Mean age (years)	48	41,5 years (15-68 years)
Disease duration	48	7,5 years (2 months-180 months)
Angioedema	48	31 (64,5%)
Symptomatic dermatographism	48	25 (52%)
Personal history of atopy	48	27 (56,3%)
Familial history of atopy	48	14 (29,1%)
Personal history of concomitant autoimmune disease	48	13 (27%)
Thyroiditis	13	9 (69,2%)
Vitiligo	13	4 (30,8%)
Familial history of autoimmune disease	48	9 (18,7%)
Positivity of ASST	48	20 (41,6%)

Table 1: Clinical data of the cohort of patients with CSU.

	N studied	Numbers (%)	Reference value
Positivity of AAbs			
Anti-TPO	48	10 (20.8 %)	> 34 U/ml
ANA	48	5 (10,4 %)	> 1:160
Rheumatoid factor	48	2 (4,1 %)	RF > 1:40

Table 2:Titers for AAbswere considered positive if anti-TPO > 34 U/ml, ANA > 1:160, and RF > 1:40.

UAS7	N studied	Numbers (%)
Activity based on UAS7 28-42: severe	48	21 (43,7%)
16-27: moderate	48	7 (14,5%)
7-15: mild	48	15 (31,2%)
1-6: well-controlled	48	2 (4,1%)
0: itch-and wheals-free	48	3 (6,5 %)

Table 3:Weekly Urticaria Activity Score (UAS7) was recorded by the patients for seven consecutive days prior to sampling day. Patients were classified according UAS7 as follows: severe CSU (UAS7 = 28-42), moderate CSU (UAS7 = 16-27), mild CSU (UAS7 = 7-15), well-controlled CSU (UAS7 = 1-6) and itch-and wheals-free (UAS7 = 0).

Figures



Figure 1: Number of patients (gender)

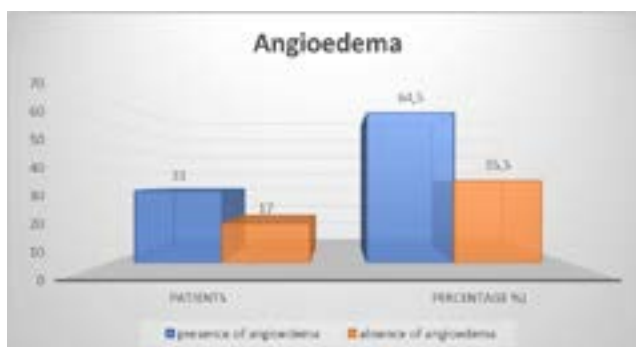


Figure 2: Presence of angioedema

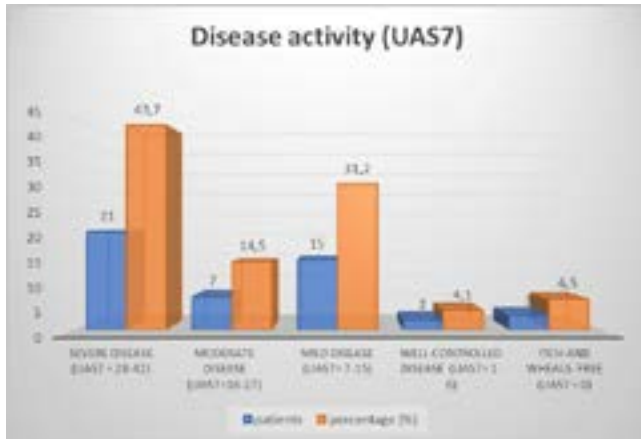


Figure 3: Disease activity (UAS7)

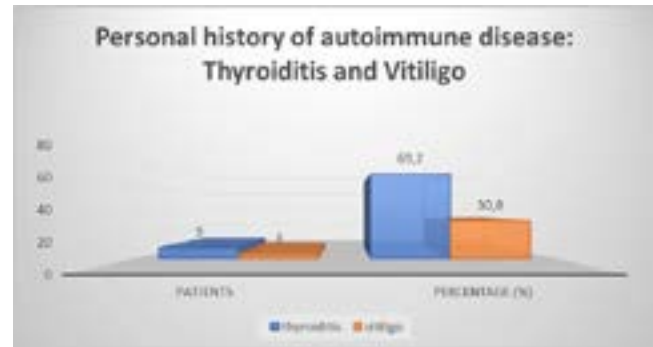


Figure 7: Personal history of autoimmune disease: Thyroiditis and Vitiligo

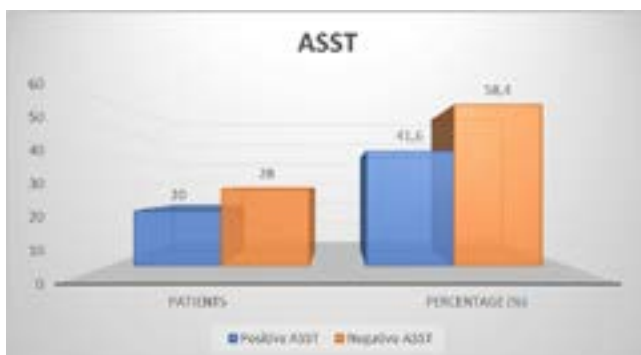


Figure 4: ASST

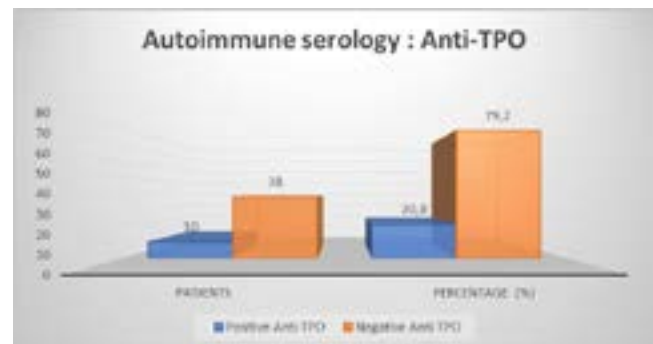


Figure 8: Autoimmune serology: Anti-TPO

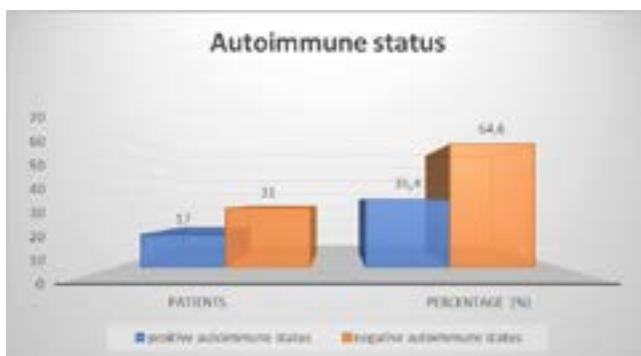


Figure 5: Autoimmune status

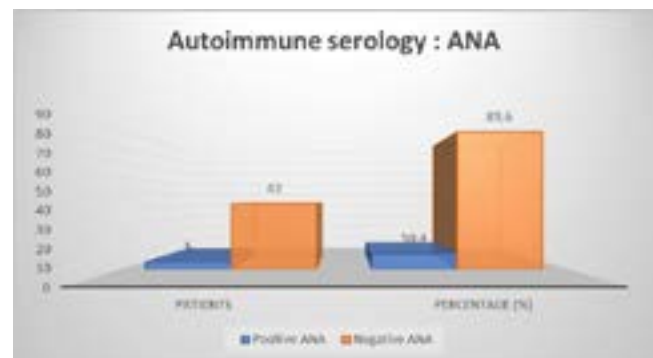


Figure 9: Autoimmune serology: ANA

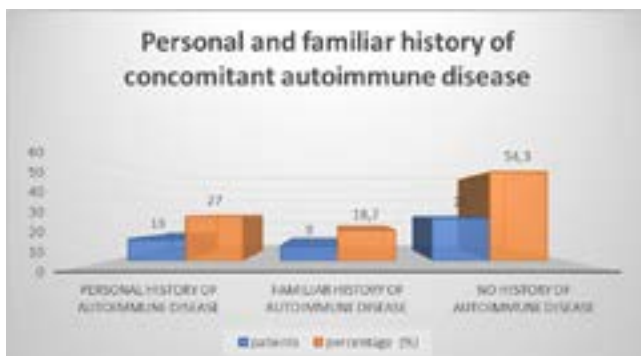


Figure 6: Personal and familiar history of concomitant autoimmune disease

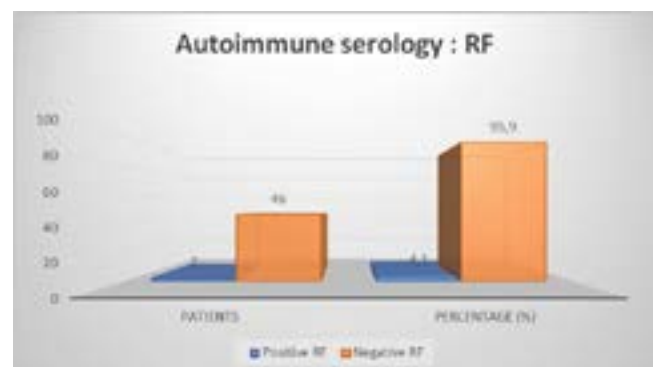


Figure 10: Autoimmune serology: RF



Figure 11: Personal and familiar history of atopy

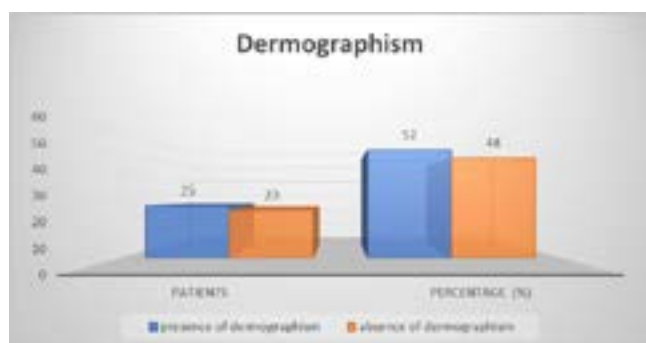


Figure 12: Personal and familiar history of dermographism

DISCUSSION

For more than 30 years, several lines of evidence argue for an auto-immune basis of CSU, or at least in a subgroup of them. In this study, we focused on associations of concomitant autoimmune disease and/or presence of AAbs (IgG-TPO, ANA and RF) and positivity of ASST. We found a relatively high incidence of autoimmune disorders and AAbs (autoimmune status) in patients with CSU. One third of the patients had concomitant autoimmune disease and/ or AAbs, mainly autoimmune thyroiditis. Moreover, a familial history of autoimmune disease was also found in 18,7% of patients. A positive wheal-and-flare reaction to ASST was found in 41,6 % of patients.

In a sentinel study conducted by Grattan et al., 12 patients with chronic urticaria were subjected to intradermal autologous serum injection (13). Seven of the 12 subjects (of whom six were female) mounted a positive wheal-and-flare reaction to this test, and fewer of these patients described a history of disease exacerbation with application of pressure when compared to patients with a negative injection test. Though theoretically performed by Grattan et al. (13), 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. Furthermore, the positivity of the test has been shown to persist even when CSU patients are in clinical remission, particularly in subjects with autoimmune thyroiditis (14).

An increased prevalence of clinical hypothyroidism (i.e., Hashimoto's thyroiditis) as well as hyperthyroidism has been found among patients with CSU, with one study estimating 23 times and seven times greater odds for hypothyroidism in female and male patients with chronic urticaria compared to control subjects, respectively (15). Patients with CSU also demonstrate higher levels of IgE anti-thyroid peroxidase (anti-TPO) antibodies relative to healthy controls, though this distribution was found to be bimodal with 39% of CSU patients exhibiting IgE anti-TPO levels similar to control subjects (IgE anti-TPO low) (16). Autoallergic mast cell activation has been shown to occur in a variety of skin disorders including atopic dermatitis (16,17). Thyroid disease is the most commonly reported autoimmune condition in patients with CU. In the literature, the frequency of thyroid autoimmunity in patients with CU encompasses a vast range of values, varying from 6.5%(18) to 57%(19). In a recent large study of 12,778 CU patients by Cofino-Cohen et al.,(15) it was found that 9.8% of patients had hypothyroidism, compared with 0.6% in the control group. In the same study (15), anti-thyroid antibodies were significantly more common in CU patients than controls. Of the patients with CU who were clinically euthyroid, anti-thyropoxidase antibodies were found in approximately 2.7% and antithyroglobulin antibodies were found in 0.6%. Treatment of concomitant thyroid disease was reported to induce remission of CU (20). Of patients with CU and hypothyroidism, RA was the most frequently identified additional autoimmune disease. The odds of having RA were 13.25 times higher in those with CU than in the control group (15). The major laboratory marker of RA, rheumatoid factor, was reported by Ryhal et al. to be significantly increased in patients with CU (21).

CONCLUSIONS

To conclude, in this prospective study, we found a relatively high incidence of concomitant autoimmune disease and AAbs. One third of the patients had concomitant autoimmune disease and/ or AAbs, mainly autoimmune thyroiditis. A positive wheal-and-flare reaction to ASST was found in more than one third of the patients. Almost

half of the patients had a personal history of atopy and presence of dermographism. Our study brings additional evidences over the utility of those clinical and biological parameters to be investigated in patients with CSU as they could be related to disease activity or autoimmunity.

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