SERUM LEVELS OF INTERLEUKIN-17, D-DIMER, IMMUNOGLOBULIN-E AND AUTOLOGOUS SERUM SKIN TEST AS SEVERITY MARKERS IN CHRONIC SPONTANEOUS URTICARIA

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disorder, in which the spontaneous appearance of wheals (hives), may be or not accompanied by angioedema, that remains above six weeks on most days of the week without any apparent trigger is characteristic. At any time, the prevalence of CSU has been suggested to be 0.5% to 1%.

The evaluation of disease activity is mainly based on medical history and clinical assessment, besides, using a number of validated questionnaires, including urticarial activity score (UAS7) and angioedema activity score (AAS). However, these questionnaires are subjective with a retrospective design. Accordingly, there is an urgent need for objective measurable indicators to assess the disease activity and monitor the treatment response.

Owing to the suggested autoimmune nature of CSU that is defined by functional Immunoglobulin (Ig) auto antibodies that are present in the blood and target either IgE or the alpha chain of IgE receptor, IgE was investigated to assess its actual role in the disease severity and activity. Additionally, the Autologous Serum Skin Test (ASST), a simple, office-based screening test for serum auto-reactivity in patients with CSU that detects auto antibodies was assessed.

The imbalance between T lymphocyte subgroups and cytokines is one of the underlying causes of the majority of autoimmune and allergy disorders. In many autoimmune diseases, including CSU, elevated Interlukin-17 (IL-17) was reported.

On the other hand, the coagulation cascade role in CSU pathogenesis was proposed. Inflammation and the coagulation cascade are intimately related, and they both activate and propagate one another. Recently, D-dimer, a fibrin degradation product, was noticed to be elevated in CSU patients.

AIM OF THE WORK

This study aimed to evaluate D-dimer, IL-17, IgE, and ASST in relation to UAS7 and AAS in patients with CSU.

PATIENTS AND METHODS

Patients: This study involved two groups of subject srecruited from the outpatient Clinic of the Dermatology, Venerology, and Andrology Department in Alexandria Main University Hospital. Sample size software (PASS 2020) and power analysis were used to determine the sample size. Group A consisted of 80 patients with CSU (Itchy wheals, angioedema, or both that appeared spontaneously, lasting ≥6 weeks from recognized causes), and group B comprised 80age and sex-matched healthy control subjects.

Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was obtained on the 20th of January 2022. An informed written consent was taken from each participant included in this study.

We excluded 1) patients on antihistamines for at least 3 days and corticosteroids or any immunosuppressive medications for 4 weeks prior to the study, 2) patients with any disease or medication used that affects the coagulation cascade (e.g. anticoagulants), 3) patients with an uncertain diagnosis of CSU during physical examination, 4) patients with any suspected case of chronic inducible urticarial.

Methods:

CSU Severity: In order to assess the disease severity, UAS7 and AAS were used. UAS7 is the summation of daily symptom scores for 7 consecutive days. UAS7 was categorized into absent (0), well-controlled (1–6),mild (7–15),moderate (16–27), and severe (28–42). With the AAS, a patient can rate their angioedema on a scale of 0 to 3 for each of the five major aspects (duration, physical discomfort, impact on activities during the day, impact on patient appearance, and the general severity of the swelling), for a total daily score ranging from 0 to 15.

Mesurment of IL-17, total IgE, and D-dimer:

Venous blood samples (6ml) were collected (from both groups) on fasting from elbow veins and divided into 3 samples. The first and the second samples are for serum IL-17 and total IgE respectively and left for clotting for one hour at room temperature before centrifugation for 15 min at 1000xg. Sera were stored frozen at -85 °C until assayed. The third one is added to an anticoagulant and used as a plasma sample for the detection of D-dimer level.

Serum IL17 level was measured by ELISA technique (E0142Hu Human IL-17 ELISA Kit, China, with a sensitivity of 1.06 ng/L) while the measurement of serum total IgE was done by means of electro chemiluminescence immunoassay “ECLIA” technique (Cobas, USA), Finally, using an automated latex agglutination method (STA-R Evolutionâ; Diagnostica Stago, Asnieres, France), plasma D-Dimerlevel was measured.

RESULTS

There were high statistically significant relations between UAS7 with serum IL-17, D-dimer, IgE, ASST, and AAS *(p ≤0.001, for all).* (Table 1)

Regarding AAS, there’s a significant positive correlation between AAS/day with D-dimer (r=0.245 and *p=0.029*), and IgE (r=0.751 and p ≤0.001). However, there was no significant correlation between AAS/day with IL-17 (p =0.748). In addition, no statistically significant correlation between ASST and AAS was found (p= 0.452). (Table 1).

Table 1: Correlations between UAS7 with serum IL-17, D-dimer, IgE, ASST, and AAS

	UAS7		AAS	
	Kruskal-Wallis test	**P value**		**P value**
IL-17	28.964	≤0.001**	0.036	0.748
D-dimer	16.812	≤0.001**	0.245*	0.029*
IgE	36.753	≤0.001**	0.751**	≤0.001**
ASST	Pearson Chi-Square	P value		P value
	21.953	≤0.001**	0.914	0.452

No correlation was found between serum levels ofIL17 and D-Dimer (p= 0.316). No correlation was found between serum levels ofIL17 and IgE (p= 0.561). No correlation was reported between serum level of IgE and D-Dimer (p= 0.938). (Table 2)

Table 2: Correlations between serum levels of IL17, D-Dimer, and IgE

	IL-17	
	r_s	P
D-Dimer	0.114	0.316
IgE	0.066	0.561
	D-Dimer	
	r_s	P
IgE	-0.009	0.938

r_s: Spearman coefficient

CONCLUSIONS

The current study data showed elevated serum levels of IL-17, IgE, and D-dimer as well as positive ASST among CSU patients, however, no correlation was reported between these biomarkers, supporting the heterogeneity of the CSU pathogenesis. Both autoimmunity and the coagulation cascade are among the heterogeneous pathways.

Moreover, all IL-17, IgE, D-dimer, and ASST were related to the disease activity. These biomarkers can be used as useful indicators for the diagnosis of CSU and for the evaluation of the disease activity and may be helpful in the diagnostic workup of CSU patients.

Regarding Angioedema, according to this study D-dimer And IgE can be considered as markers for the disease activity, but Il-17 and ASST can’t.