



Evaluation of IL-6 and IgE Levels in Iraqi Patients with Chronic Spontaneous Urticaria (CSU) in Baghdad, Iraq.

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Abstract

A skin condition known as chronic spontaneous urticaria (CSU), which lacks an obvious triggering factor, is characterized by recurrent transient wheals, angioedema, or both for longer than six weeks. The current study was focused to study compared and diagnosis CSU by using hematological and immunological parameters as (White blood cell count, eosinophils (EO), IL-6 and Total-IgE, in Chronic Urticaria patients were Clinically diagnosed by dermatologists in Specialized Center of Allergy in Baghdad/Al-Rusafa with age ranged between (11-60), as well as a control group included 40 with age ranged between (11-60). The results of demographic and clinical characteristics displayed the rate of female patients was higher than male which represented by 56.3 and 43.8% respectively. The results showed there was highly significant differences between the patients and the control in WBC, Total-IgE, IL-6 the results showed EO was higher than control but no significant difference at $p \leq 0.05$. The eosinophils percentage was high in age 51-60 and 21-30 year while those with age 41-50 and 51-60 year had highest, Total-IgE level 211.7 ± 38.96 IU/ml, 211.69 ± 38.71 IU/ml respectively but IL-6 level was highest 26.4 ± 1.77 pg/ml in patients with age group 21-30 year. WBC count in age 41-50 and 51-60 year showed highest count 9.2 ± 1.34 cell/cm³ blood, 9.3 ± 1.21 cell/cm³ blood respectively. In same time

the values of parameters were various between patients without treatment and in patients who undergoes into treatment, Finally The ROC showed the IL-6 and Total-IgE were discriminated as accurate biomarkers for CSU.

Keywords: WBC, Eosinophils (EO), IL-6 and Total-IgE, CUS and Age.

1.Introduction

Chronic Urticaria (CU) is the occurrence of symptoms for more than 6 weeks [1]the Chronic Urticaria is classified into two subclasses, the first class is Chronic Inducible Urticaria (CIndU), while the second one is Chronic Spontaneous Urticaria (CSU) is marked by angioedema and the appearance of wheals for more than six weeks in both adults and children. This subtype is appear spontaneously without unknown causes [2].There are many mechanisms that may be contributed to the pathogenesis ofCSU such as infections, food allergy, coagulation cascade and autoimmunity [3].

In CSU Type I hypersensitivity (also define autoallergy, Hypersensitivity of Type I is also known as anaphylactic hypersensitivity or acute hypersensitivity [4] is involved when antigen crosslink the immunoglobulin E (IgE) on mast cells and basophils to take out the vasoactive mediatorss [5]. IgE have a roles in allergic reactions, and its strong effecting function activated when this antibodies bind to Fc receptors FcεRI and FcεRII/CD23 [6]. Increased serum levels of IgM-anti- FcεRIα are common in patients with CSU and linked to features of autoimmunity [7]. Interleukin 6 is pro-inflammatory cytokines, which deregulated with auto-immune disorders and chronic inflammations [8] . Currently, Alasandagutti *et al.*,[9] who reported that family of IL-6 plays a vital role in CSU pathogenesis. The aim of the study was evaluate of Il-6 and total- IgE in Chronic Spontaneous Urticaria (CUS) Patients.

2.Material and methods

Patient diagnosis

Eighty patients with chronic urticaria diagnosed by dermatologists in the Specialized Center of Allergy in Baghdad/Al-Rusafa and forty healthy control samples was involved in the study from November 2021 to April 2022, divided patients into pre-treatment and post-treatment patients. All patients and controls samples underwent basic laboratory tests in addition to evaluation the levels of total IgE and IL-6 in their serum.

Collection blood samples

Eight ml of venous blood were drawn from each subject using 10 ml disposable plastic syringes in sterile conditions. (2ml) of blood was collected in EDTA tube for hematological assay Beckman analyzer counter. In the gel tube, 6 ml of blood was obtained and allowed to coagulate at room

temperature (20-25°C). After blood clotting, centrifuged at 3000 rpm for 5 minutes to obtain serum before being separated into equal parts into 3 sterile Eppendorf tubes which tightly closed and stored at -20°C for immunological testing of total-IgE (Euroimmun, Germany), IL-6 (Mybiosource, USA) by using ELISA technique.

Statistical analysis

The data was analyzed using SPSS statistical approach (Statistical Package for the Social Sciences) version-26. For quantitative variables, tested had been data for normality (Shapiro-Wilk and Kolmogorov-Smirnov Tests), and the levels have given as, (Mean \pm Stander Error). Significant differences between medians were assessed by the nonparametric tests (Mann-Whitney and Kruskal-Wallis) probability value < 0.05 ROC curve (receiver operating characteristic curve), this graph was used to discriminate whether all immunological and hematological are biomarkers or not.

3.Results and Discussion

Demographic characteristics of study:

The results of demographic and clinical characteristics showed the rate of female patients was higher than male which represented by 56.3 and 43.8% respectively, also showed 20% of patients were smoking. Finally, the mean ages of, patients 34.8 ± 1.5 as in table 1.

Table 1. Demographic and Clinical characteristics of the Participants.

Demographic characteristics	Patients N (%)	Controls N (%)
Groups	80 (50%)	40 (50%)
Gender: Male	35 (43.8%)	24 (60%)
Female	45 (56.3%)	16 (40%)
Treatment : Yes	58 (72.5%)	0 (0%)
No	22 (27.5%)	40 (100%)
Smoke: No	64 (80%)	40 (100)
Yes	16 (20%)	0 (0%)
Age (Mean \pm S.E.)	34.8 ± 1.5	34.65 ± 2.25

This findings were similar with Uysal *et al.* [10] who revealed, the 19% of patients were Smoking and the female was high than male 24/7 and age mean 47.19, also the results agreed with Hatif *et al.* [11] that found the female patients were higher than male Maurer *et al.* [12] report that the rates of chronic spontaneous urticaria that varies across Europe Central and South America, with a greater rate of females and a statistically significant difference. With an average female to male ratio of about 2-1/4, CU is one of the skin conditions with a notable female prevalence [13]. Vascular hyperpermeability has been linked to this phenomenon, which is caused by estrogen-

induced enhanced tissue expression of endothelial nitric oxide synthase. It is well-known that androgens typically have an immunosuppressive activity through a variety of mechanisms, and progesterone similarly appears to suppress immunity and inflammation. Contrarily, estrogens can promote antibody production and humoral immunity [14].

Biomarkers between CSU patients and control subject

The results showed there was highly significant difference between the patients and the control in WBC, Total-IgE, IL-6 but EO was higher than control but no significant differences at ($p \leq 0.05$) table 2

Table 2. Comparison the immunological biomarkers between study groups

Groups	N	WBC Mean± S.E	EO Mean± S.E	Total-IgE Mean± S.E IU/ml	IL-6 Mean± S.E pg/ml
Patients	80	8.14 ± 0.34 ^a	2.22 ± 0.27 ^a	198.49 ±12.6 ^a	23.92 ± 0.75 ^a
Controls	40	6.7 ± 0.22 ^b	1.89 ±0.19 ^a	32.96 ±3.8 ^b	8.7708 ± 0.57 ^b
p-value		0.011	0.548	0.0001	0.001

The different letters mean there was a significant difference while the similar letters mean there was not a significant difference.

The obtained results generally agreed with Góra *et al.*[15] mentioned the parameters (WBC,EO,IgE,IL-6) higher in patient with acute and chronic urticarial than control group , as well as agreed with Jang *et al.* [16] the serum IgE higher in the patients IgE modulates mast cell activation and releases histamine, lipid mediators, kinins, and cytokines, which contributes to the development and severity of CSU by interacting with a high-affinity IgE receptor (FcRI) found on cutaneous mast cells and basophils [17].

The results of immunological markers and age showed in table (3), the patient with age 51-60 and 21-30 year had highest eosinophils count while those with age 41-50 and 51-60 year had highest Total-IgE level 211.7 ±38.96 IU/ml, 211.69 ±38.71 IU/ml respectively but patients with 21-30 and 51-60 year showed highest IL-6 level 26.4 ±1.77 pg/ml, 25.03±2.39pg/ml respectively however the patients with different ages recorded high value levels than the control with same ages with significant differences except WBC count in age 41-50 and 51-60 year showed highest count 9.2 ±1.34 cell/cm³ , 9.3±1.21cell/cm³ respectively and eosinophils count in age 51-60 and 21-30 had highest count 2.4± 0.6, 1.99 ±0.45 respectively with no significant difference at ($p \leq 0.05$) table 3

Table 3. Biomarkers and Age Distribution in patients and control

Groups	Age Group	N	WBC Mean± S.E.	EO Mean± S.E.	Total-IgE Mean± S.E.	IL6 Mean± S.E.
Patients	11-20	13	7.9 ±0.6	3.48±1.21	177.95 ±28.20	23.38 ±1.81
	21-30	21	7.65±0.42	1.99 ±0.45	201.79 ±22.28	26.4 ±1.77
	31-40	22	7.47±0.53	1.87 ±0.28	193.07±24.04	21.38±1.12
	41-50	12	9.2 ±1.34	1.67±0.43	211.7 ±38.96	23.63±1.126
	51-60	12	9.3±1.21	2.4± 0.6	211.69 ±38.71	25.03±2.39
Controls	11-20	5	7.02±0.85	1.49±0.28	29.44±8.93	6.67±1.4
	21-30	18	7.028±0.33	1.96 ±0.27	38.63±7.36	11.09±0.78
	31-40	4	6.52±0.59	2.7±1.03	20.98±2.28	5.53±1.11
	41-50	5	6.22±0.45	1.98±0.77	26.36±5.35	6.5±1.50
	51-60	8	6.56±0.62	1.42±0.26	28.5±5.7	8.01±0.87
		P value	0.292	0.971	0.001	0.001

P value ≤0.05 means there was a significant difference between the patients and the control in same age range.

P value > 0.05 means there was not a significant difference between the patients and the control in same age range.

The results were in agreement with Chuamanochan *et al.* [18]. The most frequent cause of CU was chronic spontaneous urticaria in both groups of patients, those 67 (60-83) years old and those 35.6 (15-59) years old. However, without a statistically significant difference, the aging group had higher rates of positive autologous serum skin tests, anti-thyroid and antinuclear antibodies, increased WBC, and eosinophils than the non-aging group did. In addition, mast cells, basophils, eosinophils, and IgE are crucial elements in allergic inflammation [18].

Additionally, Hussein *et al.* [19] indicated that IL-17A may be induced by stress and may have an influence on an increase in Acute Urticaria patients' total WBC. Immediate hypersensitivity responses are started and spread by antigen-specific IgE synthesis, which is followed by IgE fixation to Fc RI receptors on mast cells and basophils. Mast cells, eosinophils and basophils are key effector cells in both innate and adaptive immunity as well as allergic inflammation [20]. this explained the patients with high eosinophils count had high IgE level too, finally same result between IL6 and eosinophils noticed in patient with same age due to IL-6 produced from eosinophils [21].

The results of Total-IgE between patients pre-treatment and post-treatment showed various results , the Total-IgE in patients pre-treatment was higher than patients post-treatment which represented 220.80 ±28.80 IU/ml and 190.03 ± 13.58IU/ml) respectively and higher than the

control group (32.96 ±3.80 IU/ml) with significant difference between those group at (p ≤ 0.05) and IL-6 between patients pre-treatment and patients post-treatment showed various results as well as IL-6 concentration in patients pre-treatment was lower than post-treatment patients (22.46±1.04 pg/ml and 24.47±0.96pg/ml) respectively but higher than the control group (8.77 ±0.57pg/ml) with significant difference between those group at p ≤ 0.05 but WBC and EO count recorded in patients pre-treatment was lower than patients post-treatment significant difference between those group at p ≤ 0.05 in table 4

Table 4 . The Comparison between pre and post treatment patients **and controls**

Group	N	Total-IgE	IL-6	WBC	EO count
Patients pre-treatment	22	220.80 ±28.80	22.46±1.04	7.64±0.42	2.59± 0.36
Patients post-treatment	58	190.03 ± 13.58	24.47±0.96	8.32±0.44	2.08± 0.34
Controls	40	32.96 ±3.80	8.77 ±0.57	6.78±0.22	1.89±0.19
p-value		a, c= 0.001 b=0.6	a, c= 0.001 b=0.4	a= 0.10, b=0.62 c=0.013	a=0.1 b=0.029, c=0.4

a-patient's pre-treatment compared with controls, b-patients pre-treatment compared with patients post-treatment, c=parameters level in patients post-treatment compared with controls.

During this study the patients were selected regardless how long have been on medicine which the section below there will be disagreement and agreements with different study due to the level of IgE will be low after treatment in month, the results showed agreement with Jang *et al.* [16] showed blood levels of free/total IgE were considerably greater in CSU patients than in healthy subjects. Serum free and total IgE levels change when using Omalizumab (Omalizumab is intended to be used as second-line therapy for the treatment of chronic spontaneous urticaria that is refractory to oral antihistamines). The levels of serum total IgE tended to rise 1 month post-treatment (P = 0.06) and gradually fall throughout the course of the 12-month treatment period without differing significantly. However, the serum total IgE level after 6 months is noticeably greater than the baseline level, suggesting that omalizumab therapy may cause a rise in serum total IgE levels. Insignificant changes were seen in serum free IgE levels throughout the course of the 12-month therapy period. The classification of individuals with CSU who are appropriate for omalizumab treatment was made easier by comparing pre- and post-treatment IgE levels and their ratios [22]. The higher quantity of allergen-specific IgE antibodies on effector cells (including basophils and mast cells) and the higher percentage of attachment to effector cells in CSU may be indicated by the higher ratio of specific IgE to serum IgE [23].

Moreover, the current results disagreed with recent study [24] showed that the serum levels of IL-6 and CCL8 pre-treatment were significantly higher than post-treatment. Wang et al [25]

reoprted the level of TNF- α , IL-6 and IL-10 in group were significantly lower after treatment . Moreover, These findings agreed with those of Fujii *et al.* [26], who observed that patients were resistant to traditional antihistamine therapy and required systemic steroids for full wheal suppression. Their increased IL-6 and CRP levels returned to normal once the urticaria subsided.. As an allergic disease, chronic urticarial is accompanied by an inflammatory reaction that secretes a large amount of inflammatory factors. TNF- α , IL-6 and IL-10 are important inflammatory factors, all of which will change to varying degrees after having an inflammatory response [27].

On the other hands, this outcome was agreed upon by [28]. The median pre-treatment IgE level in the patients was substantially lower [189.0 (1.0-1824.0)] than the post-treatment level [561.0 (2.0-4301.0)]. (P<0.001). There was no significant difference in eosinophils before and after omalizumab therapy. The patients' mean UCT score was determined to be 11.5 (3.9). Furthermore, Celik *et al.*[29] revealed the eosinophil count was greater in the post-treatment and pre-treatment groups than in the control group. In patients with CSU who required long-term Omalizumab treatment, the eosinophil-basophil ratio was high and reduced after treatment. The only statistically significant difference between the two groups that improved with Omalizumab medication in a short period of time and required long-term treatment was the eosinophil-basophil ratio.

The receiver operating characteristic (ROC)

The ROC results of IL-6 showed cut-off value is (15.0), in roc curve validity test for IL-6 dependent on clinical diagnosis and found greatest sensitivity (97.5%), specificity (95.0%), PPV(97.5%)NPV (97.4%), accuracy (93.7%) and area under curve (0.995). Overall, there is a highly significant differences between studied groups (P<0.001) as in figure 1

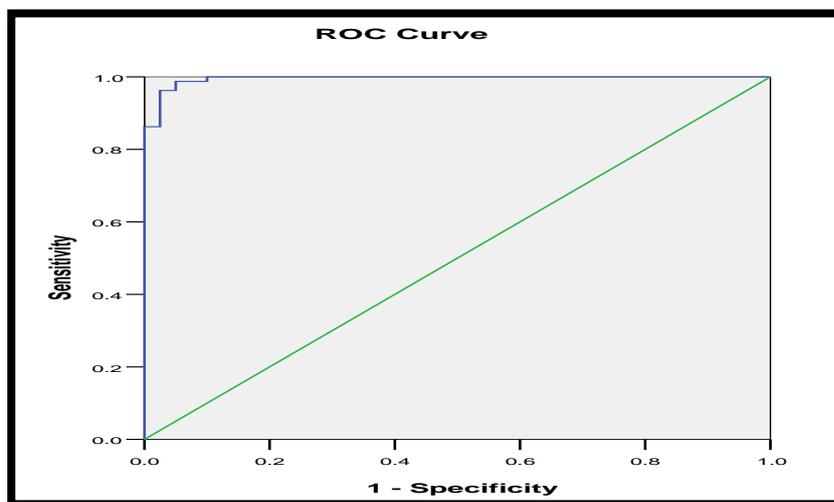


Figure 1. The ROC Curve of IL-6.

The findings were agreed to [15], the largest area under the curve (AUC) was found for IP-10 (AUC= 0.98; p 0.001), for which the optimal cut-off value determined by the Youden index was 55.10. The sensitivity and specificity of IP-10 as a biomarker of urticaria incidence were determined to be 92% and 100%, respectively. At IL-6, whose AUC was 0.96 (p 0.001) and reported same sensitivity and specificity (92% and 100%, respectively, for a cut-off point of 9.85) were demonstrated. According to ROC analysis, IL-6 has a high sensitivity and specificity as a predictor of urticarial incidence.

On the other side, the ROC results of Total IgE showed cut-off value is (78.58), in roc curve validity test for Total IgE dependent on clinical diagnosis and found greatest sensitivity (91.3%), specificity (95.0%) PPV (97.3%), NPV (85.4%), accuracy (87.4%) and area under curve (0.960). Overall, there is a highly significant differences between studied groups (P<0.001) as in figure 2

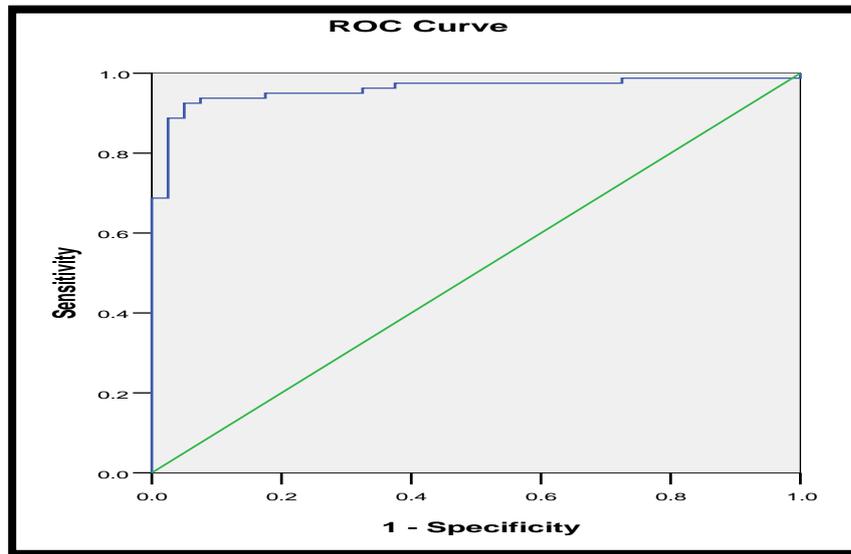


Figure 2. The ROC Curve of T-IgE

The result agreed with Jang *et al.* [16] in their study that revealed the ROC observed that the area values under AUC curve with optimum specificity and sensitivity of serum levels of total- and free- IgE for determining atopic case in patients with CSU were 0.691 and 0.730 with; 64.7% vs. 100.0% 33.3% vs. 72.7% sensitivity; specificity without considerably variations.

4. Conclusion

The obtained results showed the female was higher than male in risk of CSU which this was agreed with different previous studies , also the study showed the CSU patient had high hematological and immunological values than patients in same time the values of biomarkers was various between patients without treatment and in patients whose under goes into treatment

however during the study revealed the age from 30 to 60 year showed higher value in biomarkers than other ages Finally the ROC showed the IL-6 and IgE were discriminated as accurate biomarkers for CSU .

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