

# Research Article: The Relationship Between Serum Interleukin-6 Level and Chronic Urticaria



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## ABSTRACT

**Background:** The immunologic profile of chronic urticaria is not only important for diagnostic purposes, but also for therapeutic approaches. This study evaluated the serum levels of Interleukin-6 (IL-6), Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interferon- $\gamma$  (IFN- $\gamma$ ) in patients with chronic urticaria to find a biomarker.

**Materials and Methods:** Forty-one patients with chronic urticaria referring to the Allergy Outpatient Clinic of Rasoul Akram Hospital and 20 healthy control subjects were enrolled in the study. A questionnaire was filled and the disease activity score was determined in a one-week period for every patient. All patients underwent basic laboratory tests in addition to the Autologous Serum Skin Test. Their serum IL-6, TNF- $\alpha$ , and IFN- $\gamma$  levels were also evaluated.

**Results:** The patients were divided into two groups comprising of 20 and 21 participants according to the results of Autologous Serum Skin Tests. The serum IL-6 levels were elevated in the patients' group ( $P=0.015$ ). However, there was no significant difference between the patients with chronic urticaria and healthy controls in the serum levels of TNF- $\alpha$  ( $P=0.25$ ), and IFN- $\gamma$  ( $P=0.55$ ), neither in the exact state nor by the Mann-Whitney U test.

**Conclusion:** Serum IL-6 level was elevated in patients with chronic urticaria, but the serum levels of IFN- $\gamma$  and TNF- $\alpha$  were not significantly elevated.

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## Introduction

**C**hronic spontaneous urticaria is the recurrence of erythematous edematous pruritic papular lesions involving the superficial portion of dermis for at least 6 weeks without a known trigger. Although it is often considered a benign condition, it has a significant negative impact on the quality of life [1]. It may occur with or without angioedema. It is a disease with an important but unknown immunologic profile which calls for investigations regarding the involved cytokines.

Interleukin 6 (IL-6), with its hormone-like characteristics affecting homeostatic processes, greatly influences the cells of immune and non-immune systems. It has pro- and anti-inflammatory properties [2]. There is a wealth of knowledge about the important regulatory role of IL-6, a cytokine produced by mast cells and other cell types in the immunological and inflammatory processes [3]. There are reports on the role of the IL-6 family of cytokines in the pathogenesis of chronic spontaneous urticaria [4].

Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ) is an important mediator of chronic inflammation. Chronic idiopathic urticaria is the result of an immediate hypersensitivity phenomenon with a delayed inflammatory phase due to soluble factors such as TNF- $\alpha$ . According to studies, TNF- $\alpha$  is upregulated in the lesional and non-lesional epidermis of the patients with chronic urticaria but not in control healthy subjects. This finding suggests that the subthreshold inflammation of skin's endothelial cells induced by TNF- $\alpha$  may involve in the pathology of urticaria [4].

Interferon-gamma (IFN- $\gamma$ ) is a type II interferon with a clear action against viral infections and intracellular bacteria, as well as antitumor effects. The aberrant expression of this cytokine is described in certain autoimmune disorders [5]. Increased levels of this cytokine has been reported in chronic urticaria by Dos Santos et al. (2008) and Raap et al. (2010) [6, 7].

This study was conducted to analyze the cytokine profiles of IL-6, TNF- $\alpha$ , and IFN- $\gamma$  in patients with chronic urticaria. Therefore, specific anticytokine therapy in patients with severe chronic urticaria not responding to high dose antihistamines or generating unacceptable side effects of immunosuppressants could be a treatment option.

## Materials and Methods

### Study participants

The study population consisted of all patients diagnosed by chronic urticaria, who referred to the Allergy Outpatient Clinic of Rasoul Akram Hospital in Tehran City, Iran. The subjects were enrolled in the study from January 2010 and followed till December 2011. To include the patients in the study, chronic urticaria was defined as recurrent wheals persisting longer than 6 weeks [1]. The exclusion criteria were recurrent urticaria with physical or vasculitic features, and food- or drug-induced urticaria.

### Study design

A trained expert fellow in Allergy and Immunology completed a questionnaire for each patient and determined the disease activity score in a one-week period for them. All of the patients underwent a basic laboratory workup according to the suspected underlying diagnosis.

### Laboratory investigations

Patients were requested not to receive any forms of antihistamines, immunosuppressants, and corticosteroids for at least 10 days before skin testing and blood sampling. Healthy individuals were also selected as the control group. Venous blood samples were obtained from the patients and controls, to measure complete blood cell count with Erythrocyte Sedimentation Rate (ESR) and, C-Reactive Protein (CRP), liver enzymes, thyroid hormones and autoantibodies (anti-thyroid peroxidase and anti-thyroglobulin), antinuclear autoantibodies, and total and specific IgE. In addition, the routine urine and stool examinations were demonstrated.

### Autologous Serum Skin Test

Autologous Serum Skin Test (ASST) was performed on all of the patients with chronic urticaria. Two milliliters of venous blood was taken from the antecubital vein and collected in a sterile glass tube, allowed to clot at room temperature. Serum was centrifuged at 500 rpm for 15 minutes and intradermal injection of 0.05 mL of this fresh autologous serum was performed into the forearm 2 cm below the cubital fossa. Equal amounts of histamine and normal saline were used as positive and negative controls, respectively. A serum-induced erythematous wheal with a diameter of 1.5 mm more than the saline-induced response after 30 min was taken as positive, detected in 21 patients. The results were negative in the remaining 20 patients.

### Cytokine measurements

Commercial Enzyme-Linked Immunosorbent Assay (ELISA) (Bender Med Systems Inc., Austria) was used to measure the serum concentrations of IL-6, TNF- $\alpha$ , and IFN- $\gamma$ .

### Statistical analysis

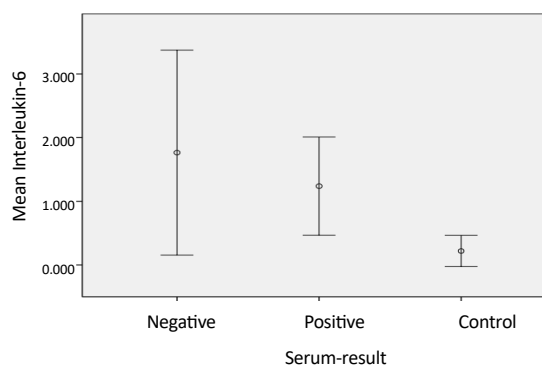
The differences between two independent groups of patients with chronic urticaria and healthy controls were compared by the Mann-Whitney U test. The Spearman correlation coefficient was used for analyzing the correlations between the obtained data.  $P < 0.05$  was considered statistically significant.

### Results

Forty-one patients with chronic urticaria referring to Allergy Clinic of Rasoul Akram Hospital were enrolled in this study. Considering the results of ASSTs (Table 1), the patients were evaluated in two groups. The control group consisted of 20 healthy age- and sex-matched subjects with the patients (mean age of 36 years). The mean age of the patients' group was 39.7 years (range: 17-65 years). Symptoms were prominent during the day in 8 (36.6%) and at night in 18 (43%) patients. The remaining 15 (36.6%) patients reported no difference between days and nights. 12 (48.8%) patients had comorbid urticaria and angioedema. A family history of atopy was found in 29 (70.7%) patients. Thyroid hormone and thyroid autoantibody serum concentration were detected in all patients. Subclinical hypothyroidism was found in 2 (5%) patients. Antithyroid peroxidase antibody and antithyroglobulin antibody were found in 12 (29.3%), and 8 (19.6%) of the studied patients, respectively.

### Serum levels of cytokines

Serum levels of IgE and cytokines, including IL-6, TNF, and IFN- $\gamma$  were measured in the patients and controls. Serum IL-6 was significantly elevated in the patients with positive ASST in comparison with healthy controls ( $P = 0.015$ ). However, as shown in Figure 1, no



**Figure 1.** Serum levels of IL-6 in patients with positive ASST, negative ASST, and healthy controls

significant difference was found between those with negative ASST, and the controls ( $P = 0.054$ ).

Serum concentrations of TNF- $\alpha$  in patients with chronic urticaria and controls were not significantly different ( $P = 0.165$ ). No significant correlation between the serum levels of TNF-alpha in patients with positive ASST and the controls ( $P = 0.06$ ) were detected. Moreover, there was no significant difference between the patients and controls ( $P = 0.26$ ). Serum IFN- $\gamma$  level was not significantly different between patients with chronic urticaria (either positive or negative ASST results) and the controls ( $P = 0.91$  and  $P = 0.36$ , respectively).

### Discussion

The current study investigated the relationship between circulating concentrations of IL-6, TNF- $\alpha$  and IFN- $\gamma$ , and the pathogenesis of chronic spontaneous urticaria. In the case of any positive correlation, they would act as serum biomarkers. Based on studies, IL-6 plays a major role in the pathogenesis of chronic urticaria by promoting the trans-signaling capacity during an inflammatory response. Therefore, the disease activity may be explained as the consequence of this chronic inflammation [5]. Mast cells, monocytes, basophils, eosinophils, activated T cells and neutrophils have all been suggested as the source of IL-6, which particularly release IL-6 in acute urticaria resistant to conventional antihistamine therapy [3].

**Table 1.** ASST results in patients with chronic urticaria

Item	No. (%)	
	Negative	Positive
ASST	20(49)	21(51)

Elevated plasma IL-6 levels are a systemic manifestation of immune activation and inflammation. However, the role of viral and bacterial products in IL-6 increments should not be ignored. We found a significant correlation ( $P=0.015$ ) between serum IL-6 levels and positive ASST results. This correlation was not significant in the patients with a negative ASST ( $P=0.054$ ). Therefore, a potential role may be suggested for IL-6, as a biomarker for disease type and severity in chronic urticaria.

Many studies supported TNF- $\alpha$  targeted therapy by considering mediator release from activated mast cells and TNF- $\alpha$  upregulation as the major factor in the pathogenesis of chronic urticaria in [8-10]. In such conditions, TNF- $\alpha$  exists in a preformed state in the mast cells and is synthesized upon mast cell activation [11], with expression throughout the epidermis. Despite the successful reports of anti-TNF- $\alpha$  treatments in patients with chronic urticaria, the increment in plasma levels of this cytokine was not confirmed in our study. We explained this finding as a profile of cytokine increase confined to the skin in chronic urticaria.

Evidence for the involvement of T cells in chronic spontaneous urticaria has been previously described [12]. A study suggested that the activation of autoreactive T cells, as the initial criterion in chronic spontaneous urticaria [1]. The same study reported that IFN- $\gamma$  responses of T cells may occur prior to autoantibody responses in the clinical course of the disease [1]. This could also be an appropriate explanation for our findings regarding IFN- $\gamma$ . We did not observe any serum IFN- $\gamma$  elevation in the patients with chronic urticaria. Therefore, we associate lack of IFN- $\gamma$  elevation to the natural trend of disease. Thus, it could signify later stages in the natural trend of chronic urticaria in our patients which made our results not positively correlated with the activity and progression of the condition.

In conclusion, it seems that IFN- $\gamma$  responses occur earlier in the course of the disease, compared to autoantibodies. This is consistent with the fact of disease initiation by T cells. Additionally, disease progression by the production of autoantibodies by B cells may be in response to an unknown or partial antigen stimulation event in the past. Therefore, perhaps in this study, the measurement of IFN- $\gamma$  has been performed too late when it had already decreased in the disease course.

There is a significant correlation between serum IL-6 level and autoimmune chronic urticaria. However, we do not recommend this cytokine profile as a serum biomarker for disease severity, activity or even classifica-

tion. TNF- $\alpha$  and IFN- $\gamma$  were two other cytokines we evaluated their serum concentrations in our study which did not demonstrate a significant correlation with chronic urticaria in the patients.

## Ethical Considerations

### Compliance with ethical guidelines

The study was approved by the Ethics Committee of Iran University of Medical Sciences. Informed consent was obtained from all study participants.

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### Authors contributions

Conceptualization: All Authors; Methodology: Mohammad Nabavi, Delara Babaie; Investigation: Delara Babaie, Houshang Gorjipour; Writing original draft: Sepideh Darougar; Writing (review and editing): All authors; and Supervision: Saba Arshi.

### Conflict of interest

The authors declared no conflict of interest.

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