



Plasma concentration of interleukin 6 (IL-6), and its relationship with circulating concentration of dehydroepiandrosterone sulfate (DHEA-S) in patients with chronic idiopathic urticaria

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Abstract

Decline in circulating DHEA-S concentration may be a phenomenon accompanying chronic idiopathic urticaria (CIU). IL-6 is a multifunctional proinflammatory cytokine which exerts a wide range of biological effects. A functional link between DHEA-S and IL-6 has been described. Therefore, the present study was performed to evaluate circulating concentration of IL-6 in patients with CIU and to study its relationship with DHEA-S and C-reactive protein (CRP) concentration. IL-6 plasma concentration was determined in 18 female non-atopic patients with CIU who had negative response to autologous serum skin test and 20 non-atopic healthy controls. Plasma concentration of IL-6 was statistically higher in CIU patients than in the control group, although all the values were found within the range of the normal subjects. CIU patients showed significantly lower DHEA-S concentration in serum than the controls. CRP concentration remained within the normal range and did not differ between the two groups. We did not find a significant correlation between concentration of IL-6 and DHEA-S, or CRP. It seems that the processes associated with CIU may be accompanied by slightly elevated plasma concentration of IL-6 and substantially decreased serum concentration of DHEA-S as compared with the healthy subjects. However, no association between IL-6 and DHEA-S concentration in the peripheral circulation of CIU patients was proved, suggesting that both phenomena may not be related to each other.

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1. Introduction

Chronic urticaria is referred to as idiopathic in absence of any identifiable causes of mast cells and basophils degranulation [1]. Psychological status, stress, as well as various neuroendocrine mechanisms may affect pathophysiology of the disease [2–4]. Different cytokines are involved in inflammatory processes associated with chronic idiopathic urticaria (CIU), including IL-6 [5–7].

IL-6 is an inflammation-associated cytokine produced by a variety of cell types, including mast cells. It is a marker of systemic inflammation and an important stimulator of

the most acute-phase protein production, including C-reactive protein (CRP) [8,9]. Moreover, IL-6 appears to play a role in conditions related to chronic stress [10,11] and contributes to coordination of adrenal response to various stimuli from the neuroendocrine and immunological system [11]. It has been well recognised that increased secretion of IL-6 occurs during various immune-inflammatory processes, including hypersensitivity reactions and autoimmune diseases [11–13].

It has been demonstrated that relative deficiency of DHEA-S is associated with various inflammatory and immune-mediated diseases, as well as stressful disorders [14–16], including chronic urticaria [17,18].

Different immuno-inflammatory and hormonal aspects of CIU were studied in the past, yet the immunologic

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and hormonal profiles of CIU patients have not been fully recognised. Because a functional link between DHEA-S and IL-6 has been suggested [19,20], the present study evaluated IL-6 plasma concentration in patients suffering from CIU who showed negative response to ASST and assessed its relationship with circulating concentrations of DHEA-S and CRP.

2. Materials and methods

2.1. Subjects

The study group consisted of 18 non-atopic, symptomatic female patients (the median age was 30.5 years, range 19–37) with chronic urticaria in whom all identified causes of urticaria had been excluded following appropriate investigation. Those with physical urticaria were excluded from the study. Their disease was characterised by duration of more than 4 months as well as recurrent hives occurring at least four times a week. Anti-histamines were discontinued 1 week before the study and none of the patients was taking any other drugs for more than 8 weeks preceding the study. All the patients showed negative response to the autologous serum skin test (ASST) performed according Sabroe et al. [21].

The control group consisted of 20 non-atopic, non-smoking healthy subjects age-, sex- and weight-matched to the patient group. All the controls presented negative ASST and did not take any medication for at least 2 weeks before the study.

All participants gave written, informed consent, and the study was approved by the University Ethics Committee.

2.2. Blood sampling and DHEA-S assay

Blood samples were obtained in the morning (8.00 a.m. to 9.00 a.m.). Serum concentration of DHEA-S was measured by automatic the electrochemiluminescence immunoassay “ECLIA” (Roche Diagnostics, Mannheim, Germany).

2.3. Assay of CRP

Plasma concentration of CRP was evaluated using the high sensitive immunoturbidimetric assay (COBAS INTEGRA C-reactive protein (Latex); Roche Diagnostics, Mannheim, Germany).

2.4. Assay of IL-6

Concentration of IL-6 antigen in plasma was measured by the enzyme-linked immunosorbent assay (ELISA) using a commercial kit (ENDOGEN, Inc., Woburn, USA).

2.5. Statistical analyses

Data were delivered as medians and ranges, and comparisons between groups were performed by Mann–Whit-

ney's *U* test. Correlation coefficient was obtained by Spearman test. *p* values lower than 0.05 were considered significant.

3. Results

We found significantly higher plasma IL-6 concentration (although all the values were within the normal range) and significantly lower serum concentration of DHEA-S in CIU female patients as compared to the healthy controls (Table 1). Plasma concentration of CRP did not differ significantly between CIU patients and the controls (data not shown). We did not find significant correlation between serum DHEA-S concentration and plasma IL-6 or CRP concentrations in CIU patients and in the control subjects (Figs. 1 and 2, respectively).

4. Discussion

Until now, there have been data demonstrating the role of IL-6 in acute [22,23] and delayed pressure urticaria [24]. In delayed pressure urticaria, IL-6 activity has been significantly higher in lesional skin than from the control sites [24]. It has been suggested that IL-6 is involved in pathogenesis of severe acute urticaria, resistant to conventional anti-histamine treatment [22]. Interestingly, it has been speculated that an increased number of total mast cells, especially tMC (tryptase-positive, chymase-negative mast cells) observed in the skin of CIU patients, might lead to the increase in proinflammatory cytokines, including IL-6 [7].

In the present study, we found statistically higher plasma concentration of IL-6 in female CIU patients as compared with healthy controls, although all IL-6 values were kept within the range in healthy subjects. Such small changes in plasma IL-6 concentration may reflect low-grade an inflammatory process in the skin of CIU patients. Elevated IL-6 plasma concentration in CIU patients may be a systemic manifestation of immune activation and inflammation in the skin, yet on the other, it is noteworthy that infection by several different viruses as well as bacterial products enhance IL-6 production [25]. It could have been then an infection we failed to identify in our patients, responsible for elevated concentration of IL-6 as compared with healthy controls.

Table 1
Serum DHEA-S concentration and plasma IL-6 concentration in CIU female patients and in healthy controls

Analysed parameters (unit)	Healthy controls (n = 20)	CIU patients (n = 18)	Statistical analysis
	Median (range)	Median (range)	<i>p</i>
DHEA-S (µg/dL)	230.9 (129–457.8)	181.7 (55–291.6)	0.023
IL-6 (pg/mL)	0.39 (0.05–0.97)	1 (0.12–2.22)	0.033

CIU—chronic idiopathic urticaria.

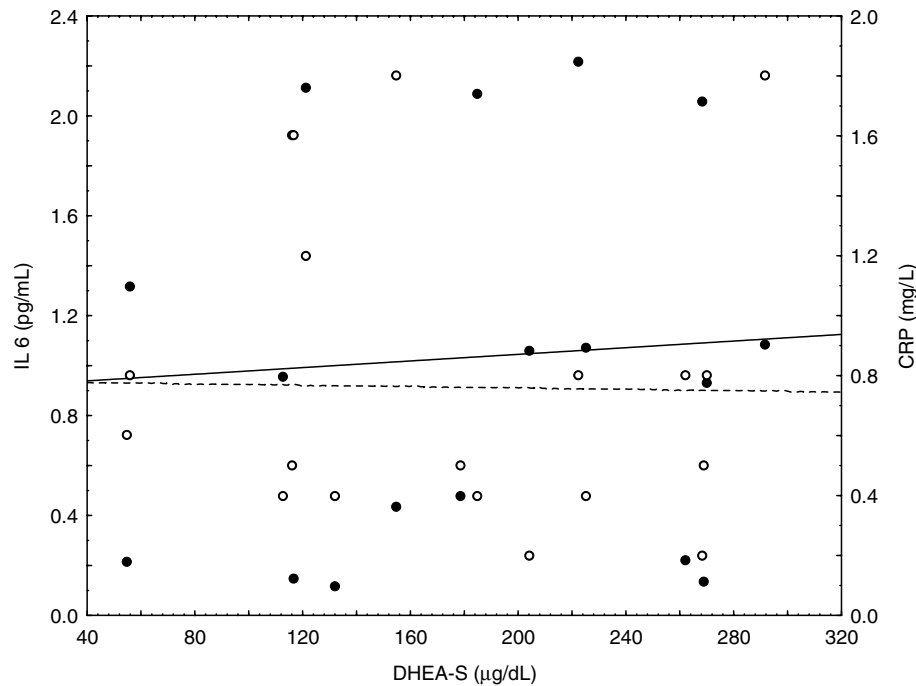


Fig. 1. Double scatter plot demonstrating the relationship between serum DHEA-S concentration and plasma IL-6 concentration ($r = 0.07$; $p = 0.79$) [solid circles and solid line] and CRP ($r = -0.02$; $p = 0.95$) [open circles and dashed line]. Each point represents an individual CIU patient. The Spearman rank correlation coefficient was used for the correlation.

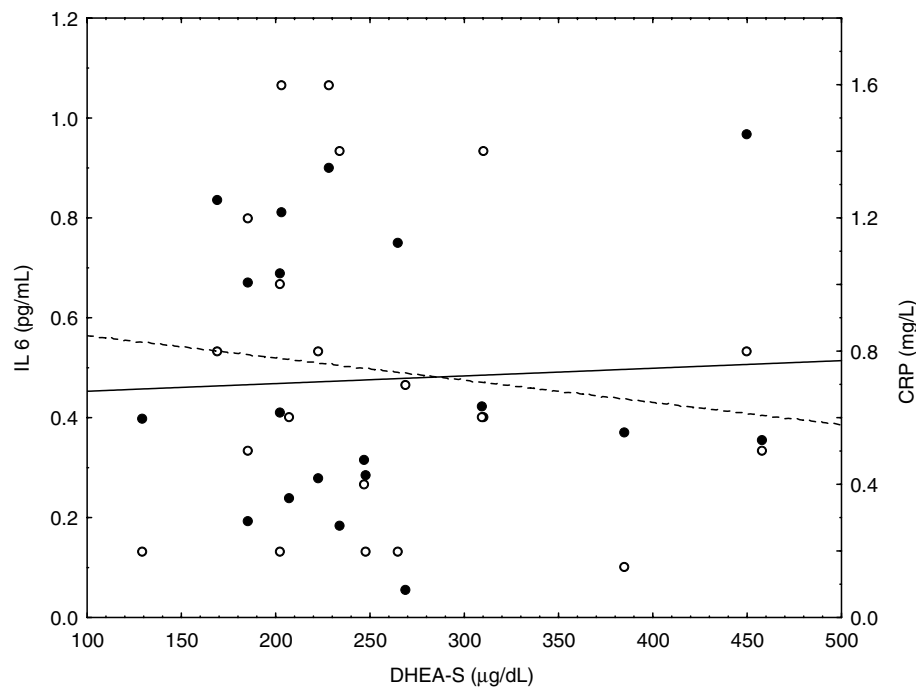


Fig. 2. Double scatter plot demonstrating the relationship between serum DHEA-S concentration and plasma IL-6 concentration ($r = -0.07$; $p = 0.78$) [solid circles and solid line] and CRP ($r = -0.12$; $p = 0.617$) [open circles and dashed line] in control subjects. The Spearman rank correlation coefficient was used for the correlation.

It is well known that IL-6 concentration is elevated in the peripheral circulation of patients with many inflammatory diseases and IL-6 stimulates the production of acute-phase proteins as well as elevated IL-6 may correlate with increases in CRP concentration [8,25]. In our study, plasma

CRP concentration did not differ significantly between CIU patients and the healthy subjects. Moreover, we did not observe any correlation between plasma concentration of IL-6 and CRP in female CIU patients. Discordance between plasma concentrations of different acute-phase

proteins is common. The patterns of cytokine production and of the acute-phase response differ in different inflammatory conditions, and not all of them increase uniformly in all patients suffering from the same disease [8].

The second question of our study asked whether there was any association between IL-6 and DHEA-S in the peripheral circulation. On one hand, it has been reported that IL-6 leads to long-term stimulation of adrenocortical steroidogenesis, including DHEA-S, suggesting its role in integration of adrenal response to stimuli from the immune and endocrine system [20]. On the other however, it has been demonstrated that DHEA is able to inhibit IL-6 secretion from monocytes, suggesting its role in regulation of this cytokine secretion [19]. Thus, it is interesting to speculate that alteration in IL-6 concentration in CIU patients might be a consequence of some changes in DHEA-S concentration and *vice versa*. It is suggested that in patients with chronic inflammatory diseases the adrenal steroid production is changed into the direction of cortisol relative to DHEA and DHEA-S, such hormonal changes being probably necessary to achieve adequate cortisol levels at the expense of adrenal androgens [26]. We speculated earlier that similar abnormalities in steroidogenesis might occur during chronic urticarial inflammation [18]. Considering the fact that IL-6 is able to stimulate androgen and glucocorticoid production [20] and the observed elevated IL-6 concentration and lower DHEA-S concentration in the peripheral circulation of CIU patients, it is interesting to speculate further that such increase in secretion of IL-6 might be necessary to preserve the adequate level of adrenal steroidogenesis.

Nevertheless, we did not find any significant correlation between concentration of IL-6 and DHEA-S in the peripheral circulation of female CIU patients, suggesting that both phenomena may not be related to each other. Thus, DHEA-S depletion in the systemic circulation of CIU patients is not probably related to slightly elevated circulating concentration of IL-6. It seems that other mechanisms may be responsible for relative DHEA-S deficiency in CIU female patients. On the other hand, Straub et al. [19] reported that serum IL-6 level was significantly inversely correlated with serum DHEA-S in healthy male and female subjects, yet Young et al. [27] stated that such correlation existed only in healthy male subjects. Moreover, an inverse correlation between IL-6 and DHEA-S concentration has been demonstrated in many chronic immune-inflammatory diseases, including colitis ulcerosa but not in Crohn's disease [28]. It should also be emphasised that our study has been limited by a small number of subjects (18) and their relatively narrow age range (range 19–37). Importantly, Straub et al. [19] studied 120 subjects within 15–80 year range. Normally, DHEA-S concentration declines with age, while IL-6 increases, therefore wider ranges of both variables might have increased the probability significant relationship observed in this study. Smaller number of the subjects evaluated might have then increased the likelihood of type II error.

In conclusion, our minor study showed some statistical differences in plasma concentration of IL-6 between female patients with CIU and healthy non-atopic subjects. In CIU female patients IL-6 plasma concentration was slightly elevated and kept within the normal range. No association between concentrations of DHEA-S and IL-6 in the peripheral circulation of CIU patients was proved, suggesting that both phenomena may not be related to each other. The endocrine alteration and its relationship with circulating levels of cytokines, including IL-6, should be a matter of further investigation, and studies extending over a larger group of patients suffering from CIU.

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