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Research Article

Correlations between serum levels of IL-17, IL-4, IL-31, IFN-gamma and etiological factors in patients with chronic spontaneous urticaria

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Abstract. Chronic urticaria is a skin disease with an important immunologic profile, which necessitates substantial investigations especially regarding the cytokine's profile. It is a well-known fact that 35-40% of patients have autoimmune chronic urticarial. Objective: to identify the presence of some etiological factors in patients with chronic urticaria, and to correlate them with interleukin 17 (IL 17), interleukin 4, interleukin 31 and interferon gamma (INF-G). Material and method: We included 59 patients diagnosed with chronic urticaria, and 15 healthy subjects. Patients with urticaria followed an etiologic screening and filled a questionnaire of disease activity (urticaria activity score – UAS, recommended by EAACI/GA2LEN/WAO Guidelines). Also, blood was collected from patients and controls, in order to determine the seric level of interleukin 17 (IL 17), interleukin 4, interleukin 31 and interferon gamma (IFN-γ). Results: The seric levels of IFN-G and IL 17 were significantly higher in patients which tested positive to autolog serum (p=0.001; p=0.01 respectively). IFN-γ value was higher in those with concomitant infectious disease (p=0.001). In those with atopic syndrome, levels of IL 31 were elevated (p=0.001). UAS was correlated with IL 17 and IL 3. Conclusion: Our study showed that the cytokines profile in chronic urticaria is a mixt one, and is related to the presence of some etiologic factors

Key Words: chronic urticaria, interleukins, interferon gamma

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Introduction

Chronic urticaria is a frequent disease that substantially affects quality of life of affected patients at a level comparable to that of patients suffering from heart diseases, on the waiting list for triple coronary artery bypass surgery (O'Donnell et al 1997). It is estimated that about 3% of the population of Western Europe suffer from chronic urticaria and the same disorder is reported in 1% of the total population of the United States. In a study conducted in Romania in 1995 (Kaplan et al 2009), a 1.9% prevalence of urticaria was assessed.

Urticaria is defined by the appearance of erythematous, edematous pruritic papular lesions that quickly appear and disappear (last up to 24 hours). It can occur with or without angioedema, when the process affects the deeper layers of the dermis or the subcutaneous tissue. When the evolution of the rash is longer than 6 weeks, it is defined as chronic urticaria.

Chronic urticaria can be caused by various agents (infections, parasitic infestations, hormonal disorders, autoimmune diseases, adverse drug reactions, atopy, food allergies), but research shows that the formation of IgG anti-FcεRIα and more rarely, anti-IgE, detected by an autologous serum skin test, or by the test assessing histamine release from mast cells, is the cause of 30-50% of cases of chronic urticaria in adults and up to 80% in children (Guttman et al 2007, Jang et al 2007, Mari 2004). Genetics also plays an important role in the occurrence of chronic urticaria, so there is a significant association between HLA class II histocompatibility antigens and chronic urticaria. The prevalence of DRB1*04 (DR4) and of DQB1*0302 (DQ8) allele is significantly increased in patients with chronic urticaria. HLA-DR4, in particular, is associated with a positive autologous serum skin test (Dillon et al 2004).

Interleukin 31 (IL-31) is a cytokine produced by activated T cells. Its structure makes it a member of the IL-6 family of cytokines. Memory T cells, able to produce IL-31, are present in the skin, where they can contribute to the occurrence of inflammation. IL-31 is considered to be an IL that can lead to skin inflammation. In experimental mouse studies, IL-31 overexpression induces pruritus and dermatitis, similar to those seen in humans (Dillon et al 2004). IL-31 was associated with atopic dermatitis (Sonkoly et al 2006, Nobbe et al 2012), contact dermatitis, and allergic respiratory diseases.

IL-17 is another pro-inflammatory cytokine secreted by Th17 cells, a subset of T helper cells, discovered in 2007. IL 17 is a cytokine which acts as a mediator in delayed-type reactions by increasing chemokine production in various tissues in order to recruit monocytes and neutrophils to the site of inflammation, similar to interferon γ. Due to the involvement of IL-17 in autoimmune diseases, there have been multiple studies on ways to inhibit its secretion, obtaining promising results in rheumatoid arthritis, inflammatory bowel disease, and especially in psoriasis .

IL-4 is an IL produced by Th cells, bone marrow stromal cells and mast cells. This IL has an important role in Th0 cell differentiation into Th2. IL-4 acts as a growth factor for mast cells. In the skin, IL-4 influences allergic reactions, mediating different reactions, particularly through its action on B and T lymphocytes and on macrophages (Banchereau et al 1993).
Interferon gamma (IFN-γ) is an acid-labile type II interferon, known to act against viral infections and intracellular bacteria, also having an important antitumor effect. Furthermore, aberrant expression of IFN-γ is found in various autoimmune diseases.
In the literature, there are several studies (Dos Santos et al 2008, Raap et al 2010) showing the increased levels of the cytokines studied in this paper in chronic urticaria, but there is few data regarding their correlation with the causes of urticaria and with UAS.
In the present study, the cytokine profile of IL-17, IL-31, IL-4, IFN- γ is analyzed in patients with chronic urticaria, together with their correlation with the degree of disease activity. There was also an analysis of their profile according to the different causes of chronic urticaria.

Materials and methods

This prospective study included 59 patients with chronic urticaria (CU) and 15 patients without urticaria or angioedema, who were part of the control group. Patients presented to the ambulatory of the Municipal Clinical Hospital between October 2007 and November 2012. Patients aged over 18 years, who had daily manifestations of urticaria, with or without angioedema, for at least 6 weeks, and who did not suffer from malignant diseases or other severe chronic diseases were included in the study. Patients were included after signing their informed consent. The study protocol was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.
Exclusion criteria were the following: other types of hives – physical urticaria, vasculitic urticaria and contact urticaria, as well as food-induced or drug-induced urticaria. Previous treatment with H1 antihistamines 4-6 weeks prior to presentation has also been an exclusion criterion.
Patients were examined by means of clinical examination and anamnesis to highlight the presence and severity of chronic urticaria. Patients completed the questionnaire to assess disease activity - urticarial activity score (UAS), recommended by EAACI/GA2LEN/WAO Guidelines1. The questionnaire consists of six questions that assess the intensity of pruritus and the number of urticarial lesions within 24 hours. The score ranges from 0 to 6 (Table 1).

Table 1. Assessment of disease activity in patients with urticarial (Zuberbier et al 2009)

Score	Papules	Pruritus
0	None	None
1	Mild (<20/24h)	Mild
2	Moderate (21-50/24h)	Moderate
3	Severe (>50/24h or large confluent lesions)	Severe

All patients underwent skin prick tests to determine atopy and the potential food allergies. We used standardized allergenic extracts (Stallergens France) at a concentration of 100 IR/ml. The test battery included the following allergens: house dust mites, grass pollen, Artemisia vulgaris and Ambrosia pollen, pollen from Salicaceae and Betulaceae, dog and cat epithelia, molds - Alternaria, Cladosporium, Candida albicans, as well as food - egg, milk, peanuts, flour, code). Skin testing was performed on the forearm using histamine extract as positive control and saline as negative control. The test result was evaluated after 15 minutes, considering the presence of papules which are over 3 mm in size as positive.
The possible presence of drug allergies has also been assessed through rigorous anamnesis, skin tests (prick and IDR) and oral provocation tests, if the first were negative.
Blood samples were extracted from patients for laboratory testing. Each patient was applied a battery of standard tests to evaluate the cause of chronic urticaria: complete blood count (CBC), CRP, antistreptolysin O antibodies, antinuclear antibodies, antithyroperoxidase antibodies, Thyroid-stimulating hormone (TSH) TSH, free thyroxine (FT4), anti-Helicobacter pylori antibodies, hepatitis B antibodies, anti-HCV antibodies, pharyngeal secretion, urine analysis, three coproparasitological exams.
Five milliliters of blood were collected to assess serum cytokines. Serum was obtained by centrifugation at 450-500 x g for 10 minutes in the first hour of collection. Part of the serum was stored at -80 C and then used for the determination of the studied cytokines: IL-4, IFN-γ, IL-17 and IL-31. Determination of serum cytokines was performed by means of ELISA (Enzyme Linked Immunosorbet Assay), using R&D System kits, Wiesbaden, Germany, as described by the manufacturing company.
A small fraction of the serum obtained was used to carry out an autologous serum skin test for all patients with CU, using saline as negative control and histamine as positive control. Each patient was injected 0.05 ml of fresh autologous and undiluted serum in the upper half of the volar face of the right forearm and the same quantity of serum was injected in the same area of the left forearm. Histamine was tested by prick method and was positioned over 3 cm under the negative control. When the difference between the papule that appeared at the site of injection of autologous serum was at least 2 mm greater than that appearing at the site of injection of saline, then it was considered positive.
For statistical analysis we used SPSS 20 software. Quantitative data were tested for normality of the distribution by means of Kolmogorov-Smirnov test. The differences in quantitative variables between two groups were assessed using T test for independent variables and the Mann-Whitney test. The differences in the percentage of a categorical variable between two groups were tested using the Chi-squared test or Fisher test. The correlation between two quantitative variables was tested using Spearman's rho coefficient. A p value <0.05 was considered to be the threshold of statistical significance.

Results

Demographic data of the subjects included in the study is shown in Table 2.

Table 2. Patient demographics

Parameter	Patients with CU	Control group	P
Age	42.7 ± 11.5	44.7 ± 9.9	P=0.4
Gender	M: 15.2% (9) F: 84.7% (50)	M: 26.6% (4) F: 73.3% (11)	P=0.4
Environment	U: 72.8% (43) R: 27.1% (16)	U: 86.6% (13) R: 13.3% (3)	P=0.3

Table 3. Characteristics of the group with CU

Parameter	Results
Activity score	4 (3;5)
Presence of angioedema	52.4% (31)
Autologous serum skin test	47.4% (28)
Presence of atopy	20.3% (12)
Elevated IgE levels	35.59% (21)
Percentage of eosinophils	2.1±1.5
Elevated levels of anti-TPO antibodies	23.7% (14)
Elevated levels of antithyroglobulin antibodies	13.5% (8)
Thyroid dysfunction	10.1% (6)
CRP >6 mg/l	16.9 (10)
Antinuclear antibodies >1/160	3.55 (2)
Presence of anti-HP antibodies	32.2% (19)
Urinary infection	8.48% (5)
Presence of hepatitis B antibodies	5% (3)
Presence of anti-HCV antibodies	6.7% (4)

As shown in Table 2, there are no statistically significant differences in terms of demographic data in the two groups of patients studied.

The study consisted of 19 (25.67%) patients from rural areas and 55 (74.32%) patients from urban areas. The mean age of patients included in the study was 43.1±10.7, with no significant differences between the two groups, and the proportion of female subjects was higher than that of males in both the group with CU and the control group.

Etiological characteristics, the presence of angioedema and the UAS score are shown in Table 3.

Median IL-31 levels were higher in the group of patients with urticaria (1086.9 pg/ml (0; 7067.3) compared with the control group (200 pg/ml (0; 3800). The difference was statistically significant (p=0.05).

IL-31 values were higher in patients with atopy (9510 pg/ml (1155; 17329) compared with those without atopy (232 pg/ml (0; 5175). This difference was highly significant (p=0.001).

IL-31 levels did not differ according to the presence of positive reaction to autologous serum, of autoimmune thyroiditis, the presence of infections of any kind or CRP (p>0.05).

Age was negatively correlated with IL-31 levels (r=-0.391, p=0.001), as well as with IL-4 (r=-0.256, p=0.04).

In this paper, IL-4 levels did not correlate with any of the etiological factors studied (p<0.05).

Median interferon γ levels were higher in the patients with urticaria (10 mg/ml (8; 14) compared with the control group (8 pg/ml; 8; 8). The difference was statistically significant (p=0.002).

IFN-γ levels were higher in subjects with a positive autologous serum skin test (12 pg/ml (8.5; 14) compared with those without this condition (8 pg/ml (8; 10). This difference was statistically significant (p=0.001).

Interferon γ levels were higher in subjects with elevated CRP (12 pg/ml (9.5; 16)) compared with those with normal CRP (8 pg/ml (8; 12). This difference was statistically significant (p=0.001).

Regarding the other variables, the presence of infection (other than Helicobacter pylori) was the variable that kept its independent influence on interferon γ levels (p=0.009).

IFN-γ levels did not differ depending on the presence of atopy in patients with rash or on that of anti-Hp antibodies (p=0.9).

Median IL-17 levels were higher in the patients with urticaria (13.8 pg/ml (0; 31.2), compared with the control group (0 pg/ml (0; 16.1). The difference was statistically significant (p=0.004).

IL-17 levels were also higher in patients with a positive autologous serum skin test, compared with patients with negative test result (p=0.01).

IL 17 levels were higher in subjects with a history of angioedema (17.3 pg/ml (1; 33.6) compared with those without this condition (0 pg/ml (0; 20.8). This difference was statistically significant (Mann-Whitney test, p=0.01).

IL-17 levels did not differ depending on CRP levels, IgE levels, the presence of atopy, the presence autoimmune thyroiditis, or the presence of infections (p>0.05).

IL 31, IL 4 and IFN-γ levels did not differ depending on the history of angioedema (Mann-Whitney test, p<0.05).

IL 31, IL 17, IL 4 and IFN-γ levels did not differ depending on total IgE levels (p<0.05).

Cytokine levels that have been studied correlated with each other as it follows – IFN-gamma levels correlated with IL-17 levels (p=0.05), IL-31 levels correlated with IL-4 levels (r=0.492, p<0.001), and other statistically significant correlations between the four cytokines have not been observed in patients with CU.

As shown in Table 3, urticaria activity score had a median value of 4. Urticaria activity score was not influenced by age (p=0.5), patient gender (p=0.3), area of origin (p=0.1), presence of autoimmune thyroiditis (p=0.7), infection (p=0.8), atopy (p=0.7), positive autologous serum skin test (p=0.6), drug allergies (p=0.7), plasma levels of IL 31 and IFN-γ (p>0.05).

Urticaria activity score was correlated with IL 17 and IL-4 levels (r=0.283, p=0.02, r=0.247, p=0.05).

Discussion

Regardless of etiology, chronic spontaneous urticaria is secondary to the change in the subjects' cytokine profile. That may explain the fact that not all patients respond to anti H1 medication, but respond to immunosuppressive drugs.

Although the most common cause is the autoimmune one, generating anti-FcεRIα IgG autoantibodies and more rarely anti-IgE antibodies, there are other etiological factors that may cause changes in the cytokine profile, favorable for the development of urticaria: various infections, atopy, thyroid disease and other autoimmune diseases. Different causes of chronic urticaria lead to different profiles of IL in these patients. There are often many cofactors involved in the production of chronic urticaria and

Table 4. Levels of the cytokines studied according to the main etiological factors identified.

		IL-4	p	Interferon gamma	p	IL-17	p	Il-31	p
Positive autologous serum skin test result	no	22.5±87.5	0.5	8 (8; 10)	0.001	13.6±20.6	0.01	3747±5360	0.8
	yes	11.1±30		12 (8.5; 14)		20.6±18.3		3957±5113	
Autoimmune tyroiditis	no	10.5±29.9	0.4	11.1±9.4	0.2	14.5±21.2	0.2	3924±5106	0.8
	yes	36.5±122		14.5±16.5		19.3±16.9		3595±5640	
Anti-HP antibodies	no	23.1±82.2	0.4	11.3±10.9	0.3	15.6±21.1	0.8	4090±5504	0.3
	yes	14.8±14.8		14.4±14.7		17±14.8		3062±4400	
Other infections	no	25.8±86.7	0.09	8 (8; 10)	0.001	13.4±19.2	0.1	3929±5596	0.8
	yes	2.8±12.8		12 (8.5; 14)		21.7±21.3		3636±4586	
Atopy	no	13.8±73.1	0.1	12.2±13	0.9	15.8±20.5	0.9	232 (0; 5175	0.001
	yes	58±60.5		11.8±5		16.6±18.1		9510 (1155; 17329)	

the occurring IL changes are secondary products of their cooperation. The role of different ILs in chronic urticaria is still not very clear. The etiological value of different factors in patients with chronic urticaria is also not clear: anti-Helicobacter pylori antibodies, other infections, anti-thyroid antibodies.

IFN-γ levels, a cytokine having mainly an immunomodulatory activity through the activation of macrophages and the suppressor role on Th2 cells, were higher in patients with CU than in the control group. Another earlier study also shows increases in IFN-gamma levels in chronic urticaria(Gao et al 2011).

Moreover, IFN-gamma levels were higher in those with a positive autologous serum skin test, compared with other causes, which supports the involvement of Th1 cells in autoimmune chronic urticaria.

IFN-γ levels were correlated with the presence of infectious factors, except for Helicobacter pylori infection, in patients considered in the study, which proves Th1 involvement in these patients as well. It is known that Helicobacter pylori infection is characterized by a Th1/Th17 type immune response (Paoluzi et al 2013). Thus, we support the idea that the occurrence of CU in patients infected with Helicobacter pylori modifies the immune response characteristic to this infection.

IL-17 levels are increased in patients with chronic urticaria, compared with the control group, which was also found in other studies (Atwa et al 2013). IL-17 levels were higher in patients who presented angioedema, urticaria severity criterion. The involvement of IL-17 in severe urticaria is also reflected in the positive correlation between IL-17 levels and urticaria activity score. Th17 is involved in autoimmune diseases, but in our study, however, IL -17 levels did not correlate with autoimmune thyroiditis. Its role in urticaria is not yet known. Our study shows that the presence of this IL increases the risk of severe manifestations, including angioedema in chronic urticaria.

The important role of IL-31 in atopic dermatitis, in particular its impact on the intensity of pruritus, is well known. In this study, IL-31 levels were significantly higher in patients with CU compared with controls, which explains its involvement in skin inflammation in this disease. Another recent study also shows elevated IL-31 levels in chronic urticarial (Rapp et al 2010). Patients with urticaria and atopy had higher IL-31 levels, IL with inflammatory function in the skin, which may lead to the conclusion that the presence of increased amounts of IL-31 in patients with atopic dermatitis favors and the occurrence of urticaria.

IL-4 levels are not significantly higher in the group of patients with CU and atopy, highlighting the reduced role of Th2 in these patients than in patients with atopy, who only have respiratory symptoms. Elevated levels of IFN gamma in patients with CU are also relevant in this respect, being known to have an inhibitory role on Th2 cells.

IL-4 levels were positively correlated with the severity of the disease, which was also the case of IL-17, suggesting the involvement of this IL in chronic urticaria, basically affecting disease severity. The correlation between IL-31 and IL-4 levels denotes Th2 membership of both cytokines. IL-4 and IL-3 have been negatively correlated with the age of patients suffering from urticaria.

The practical importance of these findings lies in the possible use of biological therapies in patients with CU who do not respond to standard treatment.

IL-31 may play an important role in chronic urticaria pathophysiology. Anti-IL-31 antibodies and IL-31 inhibitors can be administered in patients with chronic urticaria who do not respond to standard treatment, especially in those with atopy.

IL-17 levels, increased in patients with chronic urticaria, correlate with disease severity and the presence of angioedema, seriousness criterion, regardless of its etiology. From an etiological point of view, IL-17 correlates with a positive autologous serum skin test, therefore the suppression of Th17 cells can be studied in severe chronic urticaria, especially in patients with a positive autologous serum skin test.

Patients with a positive autologous serum skin test and those with infectious factors have significantly elevated IFN gamma levels, suggesting the involvement of Th1 cells in these forms of chronic urticaria.

Results were influenced by the small number of patients studied.

Conclusions

Our study shows that immunoinflammatory changes occurring in chronic urticaria are a combination of mixed Th1/Th2, as well as Th 17 lymphocyte response. Not all patients with chronic urticaria have the same profile of ILs. There is a predominant Th1 or Th2 response given by the presence of certain

etiological factors that relatively specifically modulate the immune response and determine a variation in the intensity of the manifestation of symptoms.

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