Assessment of selected interleukins (IL-6, IL-17A, IL-18, IL-23) and chemokines (RANTES, IP-10) in children with acute and chronic urticaria

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Abstract

Background

Urticarial lesions develop as a result of the activation of mast cells which, through the release of mediators, influence the formation of local inflammatory infiltrates. Changes in the expression of many cytokines and chemokines are observed in the course of urticaria.

The aim of the study was to evaluate serum levels of interleukin (IL)-6, IL-17A, IL-18, IL-23, regulated on activation, normal T cell expressed and secreted (RANTES) and interferon (IFN)-γ-inducible protein-10 (IP-10) in children with acute and chronic urticaria in comparison to healthy volunteers. Moreover, we made an attempt to identify factors predicting the occurrence and course of urticaria among the studied parameters.

Methods

We retrospectively analyzed 32 children with acute urticaria and 32 children with chronic urticaria. The control group consisted of 40 healthy children. Each patient was clinically evaluated. Serum concentrations of selected cytokines and chemokines were determined by using enzyme-linked immunosorbent assay.

Results

Patients with acute and chronic urticaria had higher concentrations of IL-6 and IL-17A ($p < 0.001$) and lower concentrations of IL-18, IL-23, RANTES and IP-10 ($p < 0.001$) as compared to the control group. IL-6 and IP-10 showed high predictive values for the development of urticaria. There was no correlation of the studied cytokines and chemokines with disease activity.

Conclusions

In children with acute and chronic urticaria, the cytokine profile differs compared to healthy subjects. IL-6 and IP-10 are useful in differentiating children with urticaria and healthy ones. The search for factors predicting the course of the disease requires further studies.

Background

Urticaria is a common pediatric dermatosis. It is characterized by the development of wheals and/or angioedema. Acute urticaria (AU) lasts less than 6 weeks and is most often associated with infectious, less commonly allergic or drug-induced factors. In chronic urticaria (CU), skin lesions persist for more than 6 weeks. CU is classified as spontaneous (CSU) and inducible (CIndU) [1]. In approximately 40% of patients, CSU may be associated with autoimmune mechanisms, but the cause often remains unknown [2]. CIndU is associated with a known trigger (e.g., cold urticaria, solar urticaria, contact urticaria) [1]. The development of urticaria is dependent on mast cell activation and degranulation. Histamine and other

mediators released by mast cells alter the permeability of the vascular endothelium, which promotes the formation of local inflammatory infiltrates composed mainly of Th (T helper) lymphocytes, granulocytes, and other immune cells [3].

The pathogenesis of chronic urticaria is related to immune mechanisms, the presence of systemic inflammation, and activation of the coagulation and fibrinolysis systems [1, 3]. Increased expression of many cytokines and chemokines is observed in patients with urticaria [4]. It is recognized that an imbalance between cellular (Th1) and humoral (Th2) responses and the activation of a Th17-type response leads to the development and maintenance of urticarial lesions [4].

Interleukin-6 (IL-6) is a multidirectional proinflammatory cytokine that regulates Th1, Th2, and Th17 responses [3]. It exhibits activity against B, T, and NK cells [5], induces mast cell proliferation and chemotaxis [3], and stimulates CRP and fibrinogen synthesis [3]. It is a frequently used marker of inflammation [6]. IL-17A (a member of the IL-17 family) stimulates the production of proinflammatory cytokines, including IL-6 [7]. Together with IL-17, IL-23 forms a common axis coordinating the action of congenital and acquired immune responses [8]. Alterations in IL-17 and IL-23 expression in patients with urticaria contribute to a disturbed pattern of Th17 lymphocyte activity, which is also observed in other autoimmune and allergic diseases such as psoriasis and atopic dermatitis [4, 9]. IL-18 plays an important role in the congenital and acquired immune response [10]. It influences the development of allergic inflammatory response by recruiting neutrophils, increasing histamine release and immunoglobulin E (IgE) production [11].

Chemokines are a group of proteins that regulate the migration of leukocytes from vessels to sites of inflammation or injury, which is crucial for the formation of urticarial lesions [12]. They affect angiogenesis, differentiation and survival of immune cells and hematopoietic stem cells [13, 14]. They are an indicator of endothelial dysfunction present in urticaria [15]. RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted/CCL5) and IP-10 (interferon-γ-inducible protein-10/CXCL10) affect the recruitment of T-lymphocytes, monocytes and other immune cells [14, 15].

The aim of this study was to evaluate serum levels of the cytokines IL-6, IL-17A, IL-18, IL-23, and the chemokines IP-10 and RANTES in a group of children with acute urticaria and exacerbations of chronic urticaria compared to healthy volunteers. Additionally, an attempt was made to identify potential predictors of the occurrence and course of urticaria among the cytokines studied.

Materials And Methods

Study design and participants

We enrolled 64 children (32 with AU and 32 with CU) aged from 2 to 17 years. The diagnosis of AU and CU was based on the EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines [1]. Patients were hospitalized in the ………. between 2013 and 2019. On admission, history and physical examination were performed. At the same time material was collected for laboratory determinations. The activity of urticaria was

evaluated according to the TSS (Total Symptom Score) [16] which is defined as the sum of the scores for the number and size of wheals and severity of pruritus. The maximum diameter of the largest wheal was assessed according to the following scheme: 0 = 0, 1 = diameter ≤ 1.5cm, 2 = diameter > 1.5cm and ≤ 2.5cm, 3 = diameter > 2.5cm. The number of wheals was estimated consecutively as: 0 = no wheals, 1 = ≤ 10 wheals, 2 = > 10 wheals, 3 = body covered with wheals. Severity of pruritus was scored as: 0 = absent, 1 = mild, 2 = moderate pruritus with slight disturbance of daily activities and/or sleep, 3 = intense itching with marked disturbance of daily activities and/or sleep. Exclusion criteria included serious general condition, anaphylaxis, hematopoietic or immune diseases, genetic syndromes, and use of antihistamines or systemic glucocorticosteroids during the 7 days preceding hospitalization.

The control group consisted of 40 healthy children matched for sex and age distribution. Children included into the control group attended the outpatient pediatric clinic for nonimmunological, noninflammatory health problems and needed venous puncture.

Laboratory methods

Sera were stored at -40°C until assays. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure the levels of cytokines. Serum concentrations of IL-6, IL-17A, IL-23, and IP-10 were measured by the use of Diaclone (France) kits. The sensitivity was respectively: 0.81 pg/ml; 2.3 pg/ml; <20 pg/ml and 5.7 pg/ml. Absorbance readings were performed using a SYNERGY/H1 (BioTek, USA). IL-18 and RANTES concentrations were determined by the use of Cloud-Clone Corp. (USA) kits with sensitivities of, respectively: 5.6 pg/ml and 0.061 ng/ml. Absorbance readings were performed using a µQuant (BioTek, USA). The obtained results were processed using Gen5v3.05 program (BioTek, USA). The procedures were carried out according to the instructions attached to the kits.

Statistical evaluation

Statistical analysis was performed using Statistica 13.1, Dell Inc. Descriptive analysis was presented as median and quartiles (Q_{25}-Q_{75}). The Kruskall-Wallis test was used to compare parameters between groups. The normality of distribution of individual parameters was assessed with the Shapiro-Wilk test. Logistic regression analysis including odds ratio estimation and 95% confidence interval was performed to determine factors affecting the occurrence of urticaria. A Receiver Operating Curve (ROC) was established to evaluate the sensitivity and specificity of the studied parameters. Correlations between selected parameters were evaluated using Spearman's rank coefficient. *p* values < 0.05 were considered statistically significant.

Results

There were no significant differences in age, gender, and BMI between the study group and control group. Demographic and clinical characteristics and selected laboratory findings in the study and control groups are shown in Table 1.

Table 1
The demographics, clinical characteristic and laboratory findings of urticaria patients compared to the control group.

Group Parameter	Acute urticaria (n = 32)	Chronic urticaria (n = 32)	Control group (n = 40)
Median age (yr) ($Q_{25} - Q_{75}$)	9.21 (7.04−12.13)	11.21 (8−14.42)	11 (7−14)
Range (yr)	2−17	2−17	3−17
Gender (M/F)	17/15	13/19	21/19
BMI (kg/m^2) ($Q_{25} - Q_{75}$)	17.85 (15.74−21.84)	18.39 (15.99−21.67)	17.35 (16.15−19.88)
Median duration of hospitalization (days) ($Q_{25} - Q_{75}$)	5 (4−6)	4 (3−5)	Not applicable (NA)
Localization of skin changes, n(%)	14 (43.8)	6 (18.8)	
- whole body	6 (18.8)	8 (25)	
- limbs	3 (9.4)	7 (21.9)	
- trunk	4 (12.5)	8 (25.0)	
- trunk and limbs	5 (15.6)	3 (9.4)	
- face			
Edema of the limbs/arthritis, n(%)	15 (46.9)	2 (6.3)	
Angioedema, n(%)	9 (28.1)	5 (15.6)	
Fever > 38°C, n(%)	10 (31.2)	0	
Abdominal pain, n(%)	4 (12.5)	0	
Wheezing, n(%)	3 (9.4)	1 (3.1)	
Respiratory tract infection, n(%)	21 (65.6)	4 (12.5)	
Other infections, n(%)	3 (9.4)	3 (9.4)	
Parasitic infection, n(%)	3 (9.4)	3 (9.4)	
Allergic disease, n(%)[a]	10 (31.2)	9 (28.1)	

*p < 0.05 in comparison to the control group

**p < 0.05 acute urticaria vs chronic urticaria

[a] positive specific IgE/skin prick tests, positive anamnesis of food and inhalation allergies

NSAIDs - nonsteroidal anti-inflammatory drugs, TSS − Total Symptom Score

Group Parameter	Acute urticaria (n = 32)	Chronic urticaria (n = 32)	Control group (n = 40)
Familial atopy, n(%)	3 (9.4)	13 (40.6)	
Antibiotic therapy, n(%)	6 (18.8)	0	
Use of NSAIDs, n(%)	2 (6.3)	1 (3.1)	
Unknown cause, n(%)	7 (21.9)	14 (43.8)	
Concomitant diseases, n(%)	21 (65.6)	17 (53.1)	
- asthma	1 (3.1)	3 (9.4)	
- atopic dermatitits	2 (6.3)	4 (12.5)	
- allergic rhinitis	3 (9.4)	2 (6.3)	
- chronic tonsillitis/tonsillar hyperthrophy	15 (46.9)	8 (25.0)	
Severity score TSS, n (%)	3 (9.4)	14 (43.8)	
Mild (0−3 points)	16 (50.0)	8 (25.0)	
Moderate (4−6 points)	13 (40.6)	10 (31.2)	
Severe (7−9 points)			
Medians of laboratory data ($Q_{25} - Q_{75}$):			
Hemoglobin (g/dL)	12.76 (12.05−13.4)**	13.63 (12.9−14.51) *	12.88 (12.21−13.81)
Platelets (x 10^3/uL)	348.5 (273.0−440.0)*	327.0 (271.0−377.5)*	274.5 (223−321)
White blood cells (x 10^3/uL)	11.18 (7.6-15.63)*/**	7.21 (5.9−9.24)	6.65 (5.59−7.92)
Neutrophil (x 10^3/uL)	6.44 (3.94−10.95)*/**	3.5 (2.72−5.37)	3.25 (2.31−3.84)
Lymphocyte (x 10^3/uL)	2.8 (2.13−3.54)	2.48 (2.1−3.38)	2.22 (1.85−3.04)

*p < 0.05 in comparison to the control group
**p < 0.05 acute urticaria vs chronic urticaria
[a] positive specific IgE/skin prick tests, positive anamnesis of food and inhalation allergies
NSAIDs - nonsteroidal anti-inflammatory drugs, TSS − Total Symptom Score

Group Parameter	Acute urticaria (n = 32)	Chronic urticaria (n = 32)	Control group (n = 40)
Neutrophil-to-lymphocyte ratio (NLR)	2.08 (1.69–3.35)*/**	1.33 (0.87–2.2)	1.22 (0.98–1.87)
Platelet-to-lymphocyte ratio (PLR)	125.28 (81.58–160.45)	119.56 (94.97–153.02)	118.87 (84.81–145.27)
C-reactive protein (mg/l)	7.66 (1.02–17.5)*	1.14 (0.55–6.44)*	0.6 (0.34–1.09)
Total IgE (IU/ml)	74.21 (44.21–171.1)	74.41 (26.46–191.55)	33.87 (20.21–89.9)
D-dimer (ng/ml)	1410.0 (690.0–2390.0)**	270.0 (260.0–390.0)	Not applicable (NA)
*p < 0.05 in comparison to the control group			
**p < 0.05 acute urticaria vs chronic urticaria			
[a] positive specific IgE/skin prick tests, positive anamnesis of food and inhalation allergies			
NSAIDs - nonsteroidal anti-inflammatory drugs, TSS – Total Symptom Score			

In the AU and CU group, regardless of disease severity, significantly higher IL-6 and IL-17A values (p < 0.001) and significantly lower IL-18, IL-23, RANTES and IP-10 values (p < 0.001) were observed with respect to the control group (CG). Lower RANTES values were also noted in patients with moderate CU compared to severe CU (p = 0,02).

Analysis including all patients with urticaria showed a positive correlation between IL-6 concentration and white blood count (WBC) (r = 0.21, p = 0.03), neutrophil-to-lymphocyte ratio (NLR) (r = 0.2, p = 0.04) and neutrophil count (r = 0.2, p < 0.05) and IL-17A concentration and CRP (r = 0.35, p < 0.001). In AU and CU patients, there was a correlation between IL-6 and CRP levels (r = 0.38, p = 0.03; r = 0.6, p < 0.001, respectively). Duration of hospitalization correlated with IL-6 levels in AU patients (r = 0.59, p < 0.001). Additionally, for CU, there was a correlation between IL-17A levels and D-dimers (r = 0,38, p = 0,03).

There were no significant correlations between the concentrations of the cytokines and chemokines studied in relation to age, BMI of the patients, and urticaria activity as determined by TSS. The comparison of cytokine and chemokine concentrations in the study and control groups is presented in Table 2.

Table 2
Comparison of the concentration of selected cytokines and chemokines in subgroups.

Group Parameter	Urticaria (n = 64)		Control group (n = 40)
IL-6 (pg/ml)	AU (n = 32)	13.27 (10.25−15.5)*	7.42
	CU (n = 32)	13.91 (11.32−15.71)*	(6.21−8.45)
	Mild CU (n = 14)	13.82 (11.4-14.53) *	
	Moderate CU (n = 8)	12.72 (11.09−14.43) *	
	Severe CU (n = 10)	15.71 (11.35−17.82) *	
IL-17A (pg/ml)	AU (n = 32)	41.5 (38.35−44.15) *	27.13
	CU (n = 32)	41.4 (38.55−48.25) *	(20.37−36.45)
	Mild CU (n = 14)	42.95 (39.6−47.6) *	
	Moderate CU (n = 8)	40.5 (34.3-45.55) *	
	Severe CU (n = 10)	41.45 (38.4−50.2) *	
IL-18 (pg/ml)	AU (n = 32)	114.2 (100.45−125.5) *	133.25
	CU (n = 32)	115.8 (102.5−129.5) *	(122.95−142.15)
	Mild CU (n = 14)	115.05 (101.5-130.1) *	
	Moderate CU (n = 8)	111.9 (101.9-123.35)*	
	Severe CU (n = 10)	123.2 (104.7-132.1)*	
IL-23 (pg/ml)	AU (n = 32)	376.5 (308−434.5) *	603.0
	CU (n = 32)	361.5 (289.0−462.0) *	(527.5−674.0)
	Mild CU (n = 14)	307.0 (289.0-364.0) *	
	Moderate CU (n = 8)	459.0 (411.0-506.5) *	
	Severe CU (n = 10)	365.0 (275.0-463.0) *	

Data presented as median (Q_{25} - Q_{75}); AU − acute urticaria, CU − chronic urticaria, RANTES - Regulated upon Activation Normal T-cell Expressed and Secreted, IP-10 - IFN-γ-inducible protein-10
*$p < 0.05$ in comparison to the control group
**$p < 0.05$ children with mild vs moderate CU
***$p < 0.05$ children with moderate vs severe CU

Group Parameter	Urticaria (n = 64)		Control group (n = 40)
RANTES (pg/ml)	AU (n = 32)	3791.0 (2896.5−4516.5) *	5822.0
	CU (n = 32)	3735.5 (3372.5−4676.5) *	(5337.5−6261)
	Mild CU (n = 14)	4190.0 (3381.0-5127.0) */ **	
	Moderate CU (n = 8)	3140.0 (2806.5−3596.0) */***	
	Severe CU (n = 10)	3871.5 (3725.0-4271.0) *	
IP-10 (pg/ml)	AU (n = 32)	48.25 (41.95−51.2) *	73.25
	CU (n = 32)	48.0 (39.95−50.35) *	(65.85−85.6)
	Mild CU (n = 14)	49.3 (43.2−50.6) *	
	Moderate CU (n = 8)	45.3 (38.1-49.15) *	
	Severe CU (n = 10)	47.45 (39.7−50.2) *	
Data presented as median (Q_{25} - Q_{75}); AU − acute urticaria, CU − chronic urticaria, RANTES - Regulated upon Activation Normal T-cell Expressed and Secreted, IP-10 - IFN-γ-inducible protein-10			
*$p < 0.05$ in comparison to the control group			
**$p < 0.05$ children with mild vs moderate CU			
***$p < 0.05$ children with moderate vs severe CU			

Logistic regression analysis was performed to determine potential indicators that may influence the occurrence of urticaria. The model was built for the AU and CU patient groups combined. It was found that urticaria was associated with higher concentrations of IL-6 and IL-17A and lower values of IL-18, IL-23, RANTES and IP-10. The parameter with the highest odds ratio was IL-6 (OR 3.35; $p < 0.001$) - detailed data are presented in Table 3.

Table 3

Logistic regression analysis of the relationship between selected factors and the occurrence of urticaria.

Parameter	OR	-95% CI	+95% CI	p
IL-6	3.35	1.98	5.66	< 0.001
IL-17A	1.24	1.14	1.35	< 0.001
IL-18	0.94	0.91	0.97	< 0.001
IL-23	0.97	0.96	0.98	< 0.001
RANTES	0.998	0.997	0.999	< 0.001
IP-10	0.76	0.68	0.85	< 0.001
OR - odds ratio, 95% CI lower and upper limits of the 95% confidence interval for the odds ratio; RANTES - Regulated upon Activation Normal T-cell Expressed and Secreted, IP-10 - IFN-γ-inducible protein-10				

On the basis of ROC curve analysis, 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 of IP-10 as a biomarker of urticaria occurrence was calculated at 92% and specificity at 100%. Similar sensitivity and specificity (92% and 100%, respectively, for a cut-off point of 9.85) were demonstrated for IL-6, whose AUC was 0.96 ($p < 0.001$). The results are shown in Table 4, the comparison of ROC curves is provided in Fig. 1.

Table 4
Receiver operating characteristic (ROC) curves analysis of selected parameters as predictors of the occurrence of urticaria.

Parameter	AUC	95% AUC CI	Cut-off	Sensitivity %	Specificity %	Youden index	p
IP-10	0.98	0.95-1.00	55.10	92	100	0.9219	< 0.001
IL-6	0.96	0.92-1.00	9.85	92	100	0.9219	< 0.001
IL-23	0.96	0.93−0.99	481.00	86	98	0.8344	< 0.001
RANTES	0.92	0.87−0.97	5241.00	92	83	0.7469	< 0.001
IL-17A	0.88	0.81−0.95	38.20	78	88	0.6563	< 0.001
IL-18	0.79	0.70−0.88	123.90	70	75	0.4531	< 0.001

AUC − area under curve, 95% AUC CI - lower and upper limits of the 95% confidence interval for AUC; RANTES - Regulated upon Activation Normal T-cell Expressed and Secreted, IP-10 - IFN-γ-inducible protein-10

Discussion

In our study, similar to previous reports, we noted higher IL-6 levels in AU [5] and CU [6] patients. This increase was previously found in patients with antihistamine-resistant urticaria [9] and in severe CU compared to patients with mild CU [16]. We did not confirm the correlation of IL-6 levels with disease activity; however, this correlation has been documented in previous work [16–18]. We noted a correlation between IL-6 levels and CRP for AU and CU and IL-6 levels and duration of hospitalization in AU. In addition, we confirmed that IL-6 concentration correlates with WBC, NLR, and neutrophil count. ROC analysis showed that IL-6 has high sensitivity and specificity as a predictor of urticaria occurence.

IL-6 is an acute phase protein closely related to the production of CRP and fibrinogen [3], whose levels are elevated during urticaria exacerbations [6, 19]. It stimulates the production of tissue factor linking coagulation and inflammation [6]. The expression of IL-6 is dependent on many factors such as coexisting chronic diseases, stress factors, trauma or infections [9], its concentration is also subject to circadian fluctuations [17].

We demonstrated significantly higher levels of IL-17A in patients with AU and CU compared to CG. In predicting the occurrence of skin lesions, this index with a relatively high specificity showed a lower sensitivity than most of the cytokines tested (88% and 78%, respectively, cut-off point 38.2). So far, most reports, like our work have shown higher IL-17 levels in CU patients [3, 9] compared to CG. Additionally,

this increase was found in patients with CU and a positive autologous serum skin test (ASST) [20]. Atwa et al. reported a correlation between IL-17 levels and urticaria severity [21], which was not confirmed by Chen et al. [4]. Contrary to previous work [7], we confirmed a positive correlation between IL-17A levels and CRP in all patients with urticaria. We also found a correlation between IL-17A and D-dimer levels in patients with CU.

IL-17A stimulates the production of proinflammatory cytokines like IL-1 and IL-6 and adhesion molecules [7]. It plays a role in recruitment of neutrophils present in urticarial infiltrate [8, 22]. Together with IL-23, it is involved in the development of autoimmune mechanisms, which is of particular importance for CU [7, 21]. IL-23 directs the early immune response and influences T-cell differentiation toward Th17 [8].

Our analysis showed significantly lower IL-23 levels in AU and CU patients with respect to CG. Different results were obtained in several papers on CU [3, 4, 20], where additionally a correlation between IL-23 levels and CU severity was shown [4]. On the other hand, Degirmenci et al. reported lower levels of IL-17 and IL-23 in patients with CU, which was explained by the effect of cytokine consumption during the ongoing inflammatory process [8]. This parameter showed relatively high sensitivity and specificity in predicting the development of urticarial lesions (86% and 98%, respectively; cut-off point 481.0).

In this study, we found significantly lower IL-18 levels in AU and CU patients compared with CG. ROC curve analysis showed that IL-18 as a marker of urticaria occurrence had the lowest sensitivity and specificity among the parameters studied (70% and 75%, respectively; cut-off point 123.9). Previous studies have shown elevated IL-18 levels in children with a single episode of AU compared to patients with recurrent urticaria and healthy volunteers [11]. Two papers reported higher IL-18 levels in adults with CU [23, 24], while other studies did not confirm such an increase or the relationship between IL-18 levels and positive ASST and urticaria activity [3, 25].

IL-18 is responsible for the regulation of Th1, Th2, and Th17 responses, stimulates mast cell degranulation, and affects the recruitment of neutrophils and eosinophils to the site of inflammation [11, 23]. It is involved in the development of many diseases including CU and autoinflammatory syndromes (cryopyrin-associated periodic syndrome - CAPS and Schnitzler syndrome) [10].

Our analysis showed lower serum levels of RANTES and IP-10 in patients with AU and CU. In the ROC curve evaluation, IP-10 proved to be a statistically valuable predictor of urticaria incidence, but no correlation with disease activity was demonstrated.

The relationship between RANTES and IP-10 has been investigated in a small number of papers finding higher levels in CU patients [15, 26], but the data are inconclusive. Puxeddu et al. showed no correlation of RANTES with disease activity [15], while Caproni et al. found no difference in IP-10 concentrations in CU patients regardless of ASST score [27].

RANTES induces histamine release from basophils and promotes differentiation and activation of mast cell progenitor cells [3, 15]. Both IP-10 and RANTES have been shown to play an important role in Th1

lymphocyte recruitment [14, 15]. IL-17 decreases lymphocyte recruitment by reducing RANTES production [28], which could indirectly explain the higher IL-17 concentrations we found with concomitantly lower RANTES levels in patients with urticaria.

The presented study is characterized by several limitations. These include the single-center, retrospective nature of the study, the limited size of the groups, and the lack of prospective determinations during the remission or convalescence phase. Urticaria activity in all patients was assessed according to the TSS scale, which does not provide more information about the patients' quality of life relevant to the overall evaluation. Cut-off points were self-selected to qualify for a group with specific urticaria severity, which may affect the interpretation of the results.

Conclusions

The cytokine profile in children burdened with acute and chronic urticaria differs significantly compared with healthy children. Among the cytokines and chemokines studied, IL-6 and IP-10 have relatively high sensitivity and specificity in assessing the risk of urticaria development. The search for factors predicting the course of urticaria requires further studies.

Abbreviations

APAACI – Asia Pacific Association of Allergy, Asthma and Clinical Immunology

AU – acute urticaria

AUC – area under curve

CG – control group

CIndU – chronic inducible urticaria

CSU – chronic spontaneous urticaria

CU – chronic urticaria

EAACI – European Academy of Allergology and Clinical Immunology

EDF; EuroGuiDerm – European Dermatology Forum

ELISA – Enzyme-linked immunosorbent assay

GA²LEN – Global Allergy and Asthma European Network

IFN-γ – interferon-γ

Ig – immunoglobulin

IL – interleukin

IP-10/CXCL10 – interferon-γ-inducible protein-10

NLR – Neutrophil-to-lymphocyte ratio

NSAIDs – nonsteroidal anti-inflammatory drugs,

OR – odds ratio

PLR – Platelet-to-lymphocyte ratio

RANTES/CCL5 – regulated on activation, normal T cell expressed and secreted

ROC – Receiver Operating Curve

Th – T-helper lymphocytes

TSS – Total Symptom Score

WBC – white blood count

Declarations

Ethics approval and consent to participate

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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Figures

Figure 1

Comparison of receiver operating characteristic (ROC) curves of IL-6, IL-17A, IL-18, IL-23, RANTES and IP-10 for predicting occurrence of urticaria.