

ORIGINAL ARTICLE

Serum TARC and CTACK concentrations in children with atopic dermatitis, allergic asthma, and urticaria

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To cite this article: Machura E, Rusek-Zychma M, Jachimowicz M, Wrzask M, Mazur B, Kasperska-Zajac A. Serum TARC and CTACK concentrations in children with atopic dermatitis, allergic asthma, and urticaria. *Pediatr Allergy Immunol* 2011; Doi: 10.1111/j.1399-3038.2011.01225.x

Keywords

asthma; atopic dermatitis; chemokines; cutaneous T cell-attracting chemokine; thymus and activation-regulated chemokine; urticaria.

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Accepted for publication 13 September 2011

DOI:10.1111/j.1399-3038.2011.01225.x

Abstract

Background: Thymus and activation-regulated chemokine (TARC/CCL17) and cutaneous T cell-attracting chemokine (CTACK/CCL27) belong to the CC chemokine family, which plays an important role in immune-inflammatory processes. It has been demonstrated that serum concentrations of TARC and CTACK are increased in patients with various allergic diseases.

Aim: To compare serum TARC and CTACK concentrations between children with different clinical manifestation of mast cell-dependent diseases, such as atopic allergy and urticaria.

Methods: A total of 87 children including 26 with mild to severe atopic dermatitis (AD), 43 children with controlled allergic asthma symptoms (treated and untreated with anti-inflammatory drugs), and 18 children with urticaria were recruited into the study. The control group consisted of 31 healthy non-atopic children.

Results: Serum concentrations of TARC and CTACK were significantly higher in children with AD than in healthy controls. No significant differences in serum concentrations of the chemokines between asthmatics, urticaria patients, and healthy controls were found. The severity of AD symptoms significantly correlated with serum CTACK and TARC concentrations.

Conclusion: These findings, in conjunction with earlier data, indicate that differences may exist in circulating concentrations of TARC and CTACK, between patients with atopic allergy and urticaria.

Atopic diseases such as asthma and atopic dermatitis (AD) are characterized by allergic inflammation of the airways or the skin in which there is overabundance of eosinophils, mast cells, and activated CD4⁺ Th2 lymphocytes. These cells perpetuate chronic inflammation by releasing a broad range of inflammatory mediators including chemokines (1). There is growing evidence that chemokines contribute to the development and maintenance of allergic processes because they coordinate the recruitment and activation of both leukocytes and residential cells at the sites of allergic inflammation (2). It has been demonstrated that CC chemokines acting via receptors expressed on T cells, eosinophils, and monocytes are implicated in the pathogenesis of AD and allergic asthma (3, 4). Thymus and activation-regulated chemokine (TARC/CCL17) is a member of the CC chemokine family. Several studies demonstrated increased TARC levels and/or its

CCR4 receptors in patients with asthma, AD, or allergic rhinitis compared with healthy non-allergic controls (4–7). Cutaneous T cell-attracting chemokine (CTACK) also belongs to the CC chemokine family and selectively attracts a subset of memory/effector T cells expressing a skin-homing cutaneous lymphocyte antigen (CLA), and it is involved in the pathogenesis of AD (8). On the opposite, CTACK (CCL27) is expressed only in the skin, and thus, it seems more useful to evaluate AD severity as compared to TARC (8). On the other hand, CCL27 acting by its receptor CCR10 is implicated in other inflammatory skin diseases such as psoriasis (9). It has been demonstrated that urticarial lesions are characterized by perivascular inflammatory infiltrate consisting of CD4⁺ and CD8⁺ T lymphocytes, eosinophils, basophils, and neutrophils (10). The mechanism regulating these cells recruitment in urticaria is not completely understood. In

addition, data regarding the behavior of chemokines in urticaria are very scarce (11). In this study, we compared serum TARC and CTACK concentrations between children with atopic allergy such as asthma and AD as well as children with urticaria.

Materials and methods

A total of 87 children (mean age 9 ± 0.8 , range 4.0–17 yr) with atopic allergy including 26 children with mild to severe AD, 43 children with allergic asthma as well as 18 children with urticaria were recruited into the study. The demographics and background characteristics of the groups are shown in Table 1.

Atopic dermatitis was diagnosed according to the criteria described by Hanifin and Rajka (12). The severity of AD was estimated according to the *SCORAD* index (ranging from 0 to 103 points) (13). The patients were not treated with any antihistamines, topical steroids or calcineurin inhibitors for at least 1 wk before enrollment into the study (only emollients were applied). They were free of any systemic steroids during the preceding 8 wk.

The diagnosis of asthma was performed according to GINA recommendations (14).

All the children had a history of recurrent episodes of the airway obstruction as well as AD symptoms, which resolved completely before age of two. Children above 6 yr of age underwent spirometric assessment and presented reversibility of the airway obstruction, as documented by positive response to a bronchodilator of at least 12% increase in FEV₁. All the children had positive skin prick tests to one or more allergens. 33 asthmatic children were treated with regularly inhaled glucocorticoids (ICS), but with different daily doses required to control symptoms (at the time of evaluation, daily budesonide dose ranged from 100 to 400 µg/day). In the remaining 10 patients with intermittent asthma, only short-acting beta-2-mimetic was used as required.

Urticaria was diagnosed and classified according to the AACI/GA2LEN/EDF/WAO guideline (15). Eleven children met the criteria for acute urticaria and seven for chronic

urticaria. In all cases, any known causes of urticaria were ruled out by appropriate investigations. Each patient underwent the following routine laboratory tests: full blood count, urine analysis, erythrocyte sedimentation rate, C-reactive protein, serum glucose, hepatic functions, and creatinine examination. In addition, stool examination for parasites and *H. pylori* antigen, hepatitis serology (anti-HCV, HBsAg), rheumatoid factor, antistreptolysin-o, immunoglobulins, antigliadin antibodies (both IgA and IgG class), anti-endomysium antibodies, complement, anti-nuclear and antithyroid microsomal antibodies, thyroid function tests (Thyroid-stimulating hormone (TSH) and free thyroxine (fT4)), chest X-ray and abdominal ultrasonography were performed. In spite of extensive studies, no cause was found in seven patients with urticaria (acute urticaria – three children; chronic urticaria – four children). The identified possible causes of urticaria were the following: food allergy (one patient), lamblia (two), recurrent upper respiratory infection (five) – for acute urticaria and lamblia (one), chronic urinary tract, or otitis infection (two) – for chronic urticaria.

All the children with urticaria had severe symptoms and did not receive any medication during the blood collection. Their daily urticaria activity scores (UAS) were measured by the assessment of wheals and pruritus on a scale of 0–3 (sum of score: 0–6). A daily UAS of 0–2 was considered to represent mild urticaria, 3–4 moderate, and 5–6 severe urticarial symptoms (15).

The control group consisted of 31 healthy non-atopic children (mean age 9.4 ± 4.26 , range 5.0–17 yr).

The study was approved by the Ethics Committee of Medical University of Silesia, Katowice. Written informed consent was obtained from the parents of all patients.

Measurements of TARC and CTACK concentrations

Blood was obtained in the morning (7.00 a.m. to 8.00 a.m.; in the fasting state). Serum samples were obtained from clotted blood following centrifugation at 1300 g at 4°C for 10 min and subsequently stored at –40°C until analysis. The

Table 1 Demographic and clinical characteristics of patients with AD, asthma, urticaria, and the control group

	AD	Asthma	Urticaria	Control group
No	26	43	18	31
Age (yr)	9.7 ± 3.5	8.47 ± 3.81	10.52 ± 4.43	9.4 ± 4.26
Sex M/F	13/13	23/20	7/11	17/14
Serum total IgE IU/ml	421 [91–1058]*	240 [70–471]*	63 [27–100]	35 [16–58]
Eosinophil count/µl	$483.3 \pm 572^\dagger$	296.73 ± 195	180.66 ± 112	157.86 ± 63
Duration of disease (yr)	3.55 ± 2.0	5.01 ± 3.26		
<i>SCORAD</i>	42.24 ± 28			
FEV ₁ (%)		84 ± 23		
FEV ₁ /FVC		81 ± 15		
Daily dose of ICS (µg)		282 ± 296		
C-reactive protein (mg/l)	2.9 ± 11	5 ± 11	$8.64 \pm 15.17^\ddagger$	1 ± 1.2

ICS, inhaled glucocorticoids; AD, atopic dermatitis.

Values presented as mean $\pm$ s.d. or median and quartiles (serum total IgE).

*AD and asthma vs. control $p < 0.05$, † AD vs. control $p < 0.05$, ‡ Urticaria vs. control.

serum concentrations of TARC and CTACK were measured in duplicates by sandwich enzyme immunoassays (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol. The lower limits of detection for these chemokines were 1.6 and 62.5 pg/ml, respectively.

Other laboratory investigations

The serum concentration of total IgE was measured by ELISA using a commercial kit (Allergopharma, Reinbeck, Germany) according to the manufacturers' instructions. The blood eosinophil counts were determined using an automatic hematology analyzer. Serum CRP (C-reactive protein) concentration was measured by the turbidimetric latex agglutination method (CRP-Latex; BioSystems SA, Barcelona, Spain) with a detection limit of 1.0 mg/l. Elevated serum CRP was defined as higher than 5.0 mg/l.

Skin prick tests

Allergic sensitization was evaluated by skin prick testing with a panel of common inhalant allergens (Allergopharma). Saline and histamine solutions were used as negative and positive controls, respectively. A wheal of diameter greater by at least 3 mm than the negative control was accepted as a positive response.

Statistical analysis

Statistical analyses were performed using software package (Statistica, version 9.0 software package StatSoft, Cracow, Poland). Kruskal–Wallis and Mann–Whitney *U*-tests were used for comparisons between groups. Correlations between variables were tested using Spearman's test. *p* values < 0.05 were considered statistically significant.

Results

Serum chemokines concentrations in patients and healthy subjects

In children with AD, serum concentrations of TARC and CTACK were significantly higher than in healthy controls (Table 2, Fig. 1a,b). No significant differences in serum con-

Table 2 Serum concentrations of TARC and CTACK in the examined groups

	TARC mean $\pm$ s.d. (pg/ml)	CTACK mean $\pm$ s.d. (pg/ml)
AD	867.35 $\pm$ 482*	918.5 $\pm$ 266*
Asthma	575 $\pm$ 421	769 $\pm$ 221
Urticaria	518.3 $\pm$ 442	693 $\pm$ 128
Control	408.87 $\pm$ 313	684 $\pm$ 178

TARC, Thymus and activation-regulated chemokine; CTACK, cutaneous T cell-attracting chemokine; AD, atopic dermatitis.

*AD vs. control *p* < 0.05.

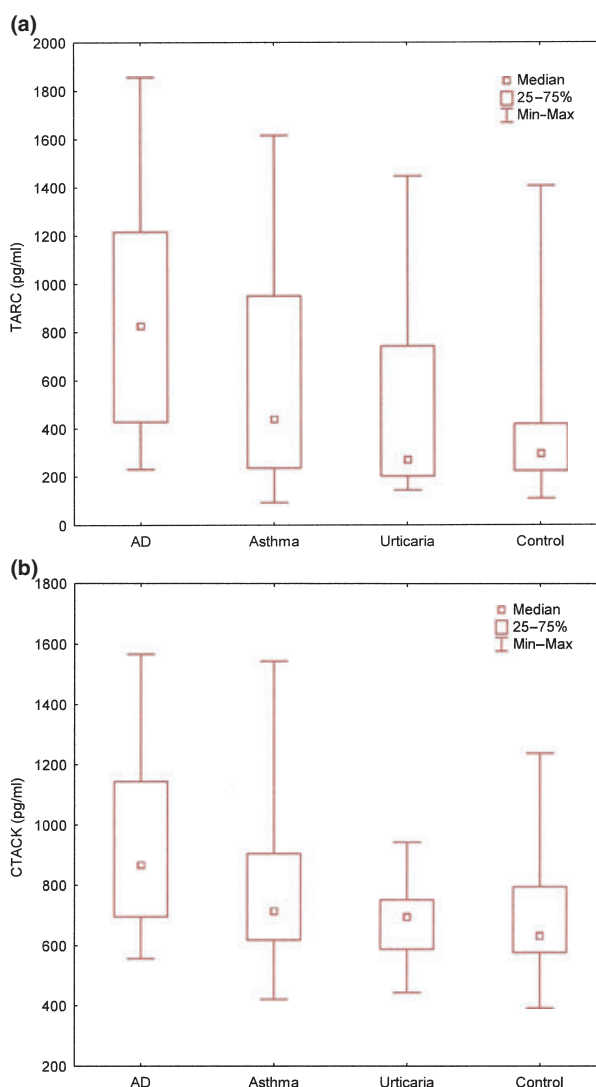


Figure 1 Serum concentrations of thymus and activation-regulated chemokine (TARC) and CTAC in the examined groups. (a) TARC (*p* < 0.05, atopic dermatitis [AD] vs. control). (b) CTAC (*p* < 0.05, AD vs. control).

centrations of TARC and CTACK between patients with controlled asthma symptoms and healthy controls were found, although TARC serum concentration tended to be higher in asthmatic children than the controls. Also children regularly treated with ICS had similar chemokines concentrations as compared to asthmatics untreated with ICS-intermittent asthma (data not shown). There were no significant differences in serum concentrations of TARC and CTACK between patients with urticaria and healthy controls. Also serum TARC (acute urticaria: 514.15 $\pm$ 476 and chronic urticaria: 524.82 $\pm$ 420 pg/ml) and CTACK concentrations (acute urticaria: 683.56 $\pm$ 98 and chronic urticaria: 699.89 $\pm$ 148 pg/ml) were similar in the both subgroups (*p* > 0.05).

IgE and CRP concentrations and eosinophil count in the patient and control groups

The eosinophil count was significantly higher in patients with AD than in the healthy controls. Total serum IgE concentration was significantly higher in both AD and asthma patients as compared to healthy subjects. Although not statistically significant, children with urticaria had also a higher serum IgE concentration. There were no significant differences in serum CRP concentrations between asthma, AD, and the control groups. In contrast, children with urticaria had significantly higher CRP concentration than healthy controls (Table 1).

Correlations in AD and asthmatic groups

Significant correlations were found between the AD severity index score and serum concentrations of CTACK and TARC (Fig. 2a,b) [the correlation was performed for 24 patients due to the fact that SCORAD values were not reliably assessed for two children].

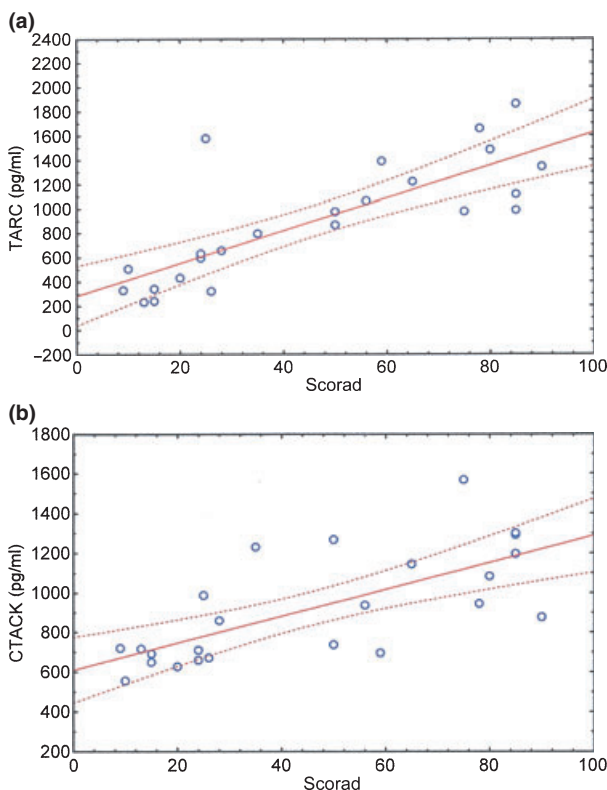


Figure 2 Association between the severity of atopic dermatitis and serum thymus and activation-regulated chemokine (TARC) and cutaneous T cell-attracting chemokine (CTACK) concentrations. (a) Positive correlation between SCORAD index and serum TARC concentration ($r = 0.699$, $p < 0.05$). (b) Positive correlation between SCORAD index and serum CTACK concentration ($r = 0.792$, $p < 0.05$).

Severity of AD symptoms was positively correlated with eosinophil count and total serum IgE concentration (data not shown).

Significant correlations were found between serum concentrations of total IgE and TARC and CTACK ($r = 4.0$, $p < 0.05$; $r = 0.3$, $p < 0.5$, respectively). In addition, weak positive correlation between serum concentrations of TARC and CTACK and eosinophil count was observed (for both, $r = 0.2$, $p < 0.05$).

Serum TARC and CTACK concentrations were negatively correlated with the age of children with AD ($r = -0.27$, $r = -0.25$, $p < 0.05$, respectively).

Significant inverse correlation was observed between FEV₁ value and serum TARC concentration ($r = -0.36$, $p < 0.05$) in asthmatic children (Fig. 3). In contrast, no correlation was found between CTACK and FEV₁ values ($r = 0.02$).

Discussion

Similarly to other reports, we found that serum concentration of TARC/CCL17 is elevated in children with AD (6, 16, 17). The TARC chemokine is expressed by various cells including epidermal keratinocytes, mononuclear cells, fibroblast, platelets, and activated bronchial epithelial cells (8). In skin lesions from patients with AD, immunoreactive TARC was present in keratinocytes, vascular endothelial cells, T cells, DCs, and infiltrating cells (8, 18). TARC can be up-regulated by proinflammatory cytokines such as tumor necrosis factor- α , interleukin (IL)-1, and interferon- γ (19). Both IL-4 and IL-13 also promote TARC expression (20).

In our study, serum concentration of TARC correlated positively with AD severity measured by SCORAD index, as well as with the number of eosinophils and total IgE concentration. This confirms previous observations demonstrating that the monitoring of circulating TARC concentration is a useful marker of the disease severity (4, 18, 21–23). Recently, strong association between serum TARC concentration and natural course of childhood AD (newly developed, regressed, and maintained AD) was found. Furusyo et al. (24) observed that in children with regressed AD symptoms, serum concen-

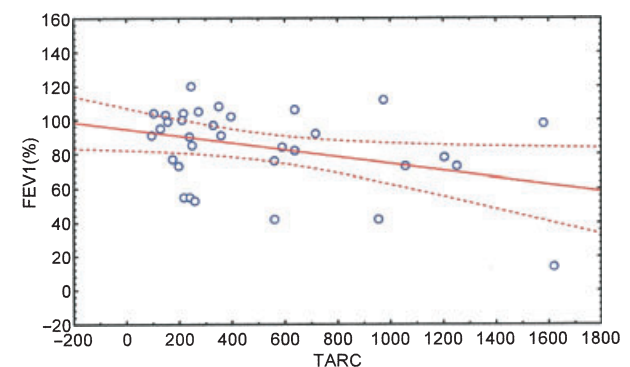


Figure 3 Inverse correlation between FEV₁(%) and serum thymus and activation-regulated chemokine concentrations ($r = -0.36$, $p < 0.05$) in children with asthma.

tration of TARC was reduced to a concentration observed in healthy subjects. In addition, it has been demonstrated that in adult patients with AD, TARC concentration decreased after treatment, in parallel with the improvement of clinical symptoms (21, 25). Moreover, serum TARC concentration from umbilical cord may be a predictive marker for AD in infancy (26). The age-related difference in serum TARC concentration was observed by others (6, 25) as well as in our study.

It is assumed that TARC, via the recruitment of Th2 cells expressing chemokine receptor (CCR)-4 in the site of allergic inflammation, is involved in the pathogenesis of allergic Th2-mediated diseases. Indeed, TARC is strongly up-regulated in serum and/or airways in both pediatric and adult patients, in particular during exacerbation or exposition to a relevant allergen (5, 7, 27–31). In some studies, increased TARC concentration was positively correlated with total IgE concentration (5) and disease severity (29, 30, 32). In other, elevated TARC concentration was not related to asthma severity score, lung function, and other inflammatory markers (5, 27).

In the present study, serum TARC concentration in children with well-controlled asthma was slightly, but not significantly elevated as compared to healthy controls. On the other hand, a weak inverse correlation between TARC and FEV₁ was observed. Correlation between TARC expression and airways obstruction was previously reported in a few studies (29, 30). An inverse correlation between plasma TARC concentrations with peak expiratory flow rate during asthma exacerbation in children was found (30). Moreover, elevated TARC expression in the epithelium and submucosa of bronchial biopsies from asthmatics correlated inversely with FEV₁ as well as with the percentage of submucosal CD4⁺ T cells expressing CCR4 (29). In addition, mouse models of allergic inflammation have shown that neutralization of TARC inhibits T cell and eosinophil infiltration into the lung and bronchial hyper-responsiveness (33).

In the present study, children were treated with different doses of ICS; it may partially explain why a significantly higher TARC concentration was not observed in our asthmatic children. It has been demonstrated that the treatment of asthma with ICS significantly down-regulates bronchial TARC expression, which is accompanied by reduction in infiltration of the airways by inflammatory cells (34). It has also been shown that plasma TARC concentration was higher in pediatric asthma patients without ICS treatment compared with those treated with inhaled steroids (5). In our study, children with well-controlled asthma according to GINA recommendations both regularly treated with ICS and with intermittent asthma (untreated with ICS) had similar chemokine serum concentration.

Plasma TARC concentration was significantly higher in patients with persistent asthma than those with intermittent disease (32). In both children and adults with asthmatic exacerbations followed by prednisolone treatment, plasma TARC concentration decreased to that of healthy volunteers and remained suppressed after discontinuation of systemic corticosteroids (27, 30). No comparison of TARC concentrations before and after ICS treatment in our asthmatic children

(blood was not taken before and after the therapy) may be a drawback of this study.

Although many studies highlighted an important role of TARC in AD pathogenesis, it seems that the CTACK/CCL27 chemokine may be more useful for evaluating severity of the disease, particularly in patients with coexisting atopy. CTACK is expressed only in the skin (especially in epidermal keratinocytes), but not in other organs (8). Therefore, serum CTACK concentrations may reflect an overflow of the locally produced chemokines into the systemic circulation. CTACK attracts skin-homing T cells of both Th1 and Th2 subtypes expressing CCR10, positive for skin-homing CLA⁺ (35).

In the present study, we found that serum CTACK concentration is elevated in children with AD and significantly correlated with the disease severity. Our results confirm earlier observations conducted in children and adult with AD (36, 37). In addition, in children with AD, significant association was found between serum CTACK concentration and eosinophil count as well as total IgE concentration, which confirms previous results published by Song et al. (6). Similarly, significant relationship between TARC expressions and the allergic markers in AD has been documented by the authors as well as in other studies (4, 6, 18). Both TARC and CTACK are specific chemoattractants for T_H2 subtypes producing cytokines, such as IL-4, IL-5, and IL-13, which induce IgE production and eosinophil activation, which might account for the results obtained.

Histology of chronic spontaneous urticaria (both idiopathic and autoimmune) demonstrates a perivascular non-necrotizing infiltrate of CD4⁺ lymphocytes consisting of a mixture of T_H1 and T_H2 subtypes, together with monocytes, neutrophils, eosinophils, and basophils. These cells are recruited as a result of interactions with C5a, cell-priming cytokines, chemokines, and adhesion molecules (11). Very scarce data are available on the behavior of different immuno-inflammatory mediators in children with urticaria. Therefore, in the present study, we also sought whether deregulation regarding T_H-2 chemokine profile can be detected in children suffering from urticaria. In our study, serum concentrations of TARC and CTACK in children with urticaria did not differ from healthy children. Similarly Caproni et al. (11) observed no significant differences in serum TARC concentration between adult urticaria patients and healthy controls.

Taken together, these findings, in conjunction with earlier data, lead to some interesting consideration regarding the differential behavior of serum TARC and CTACK concentrations in children with various mast cell-dependent inflammatory diseases. So far, evidence is lacking to prove that increased release of the chemokines into the peripheral blood occurs in cases of all the diseases, regardless of their clinical expression or severity. Similarities should be noted between various atopic allergic diseases as well as urticaria, but there are also differences; thus, the profiles of inflammatory mediators, including the chemokines, may appear different. In addition, it should be taken into account that different types of therapy may influence behavior of the chemokines.

There are several limitations of our study. Firstly, a cross-sectional design of the study limits the validity of interpretation of the possible effect of ICS therapy on examined parameters in children with asthma. Secondly, our study involved a relatively small sample size, particularly children suffering from urticaria. Thirdly, the lack of subjects with disappeared AD symptoms without concomitant allergic disease may also be considered as a drawback of this study.

In conclusion, serum concentrations of TARC and CTACK were significantly higher in AD children than in healthy controls. No significant differences in serum concen-

trations of TARC and CTACK between asthmatics, urticaria patients, and healthy controls were found.

These findings, in conjunction with earlier data, indicate that differences may exist in circulating concentration of TARC and CTACK between patients with distinct clinical manifestation of atopy and urticaria.

Acknowledgment

This study was supported by a research grant KNW-2-205/08.

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