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Associations of the Novel Chemokine-Based Diagnostic Biomarker Panel with Different Phenotypes of Atopic Dermatitis in Children

Взаимосвязь новой диагностической хемокиновой панели биомаркеров с различными фенотипами атопического дерматита у детей

Abstract

Introduction. Serum total immune globulin E, thymus and activation-regulated chemokine (CTACK), and cutaneous T-cell attracting chemokine (TARC) are known as contributing to the pathophysiology of atopic dermatitis. Still, there is the data ambiguity regarding the associations of serum biomarkers with the clinical manifestations of the disease.
Purpose. To detect the associations of total immune globulin E, thymus and activation regulated chemokine, and cutaneous T-cell attracting chemokine with different phenotypes of atopic dermatitis in children – alone and combined with other atopic comorbidities (seasonal allergic rhino-conjunctivitis, perennial allergic rhinitis, bronchial asthma).
Materials and methods. The main group consisted of 39 patients aged from 3 to 18 years suffering from atopic dermatitis alone and with comorbid atopic disorders – seasonal allergic rhino-conjunctivitis, perennial allergic rhinitis, and bronchial asthma. The control group consisted of 47 children aged from 3 to 18 years, non-atopics, suffering from the gastro-intestinal tract disorders. The patients of both groups were tested for the serum concentrations of the above-mentioned serum biomarkers.
Results. There were detected significantly higher levels of total serum immune globulin E and CTACK in atopic patients if compared to controls. Serum TARC showed no significant differences between the main and control group; still, it had significant direct associations with the degree of severity of atopic dermatitis phenotypes alone and combined with other atopic disorders in general and with clinical index "scoring atopic dermatitis" in particular. It had also significant indirect associations with age in patients of the main and control groups. Serum total immune globulin E and CTACK had significant direct associations with all the studied atopic dermatitis phenotypes. There is a strong perspective of combining the serum total IgE, TARC and CTACK as the effective biomarker panel for assessing the intensity of inflammation within different atopic dermatitis phenotypes.
Conclusions. Combined use of serum total immune globulin E, thymus and activation-regulated chemokine and cutaneous T-cell attracting chemokine is the novel perspective chemokine-based

НА ПЕРВУЮ | НА СЛЕДУЮЩУЮ | НА ПРЕДЫДУЩУЮ | К СОДЕРЖАНИЮ

panel for assessing the degree of severity in patients that suffer from different phenotypes of atopic dermatitis alone and combined with comorbid atopic disorders.
Keywords: atopic dermatitis, children, phenotypes, associations, biomarkers, total IgE, thymus and activation-regulated chemokine, cutaneous T-cell attracting chemokine.

Резюме

Введение. Общий сывороточный иммуноглобулин Е, тимусом и активацией регулируемый хемокин (ТАРХ) и кожный Т-клетки аттрактирующий хемокин (КТАХ) известны как факторы патогенеза атопического дерматита. Тем не менее существует неоднозначность данных относительно ассоциаций данных биомаркеров с клиническими проявлениями вышеупомянутого заболевания.
Цель. Выявить взаимосвязь общего иммуноглобулина Е, тимусом и активацией регулируемого хемокина и кожного Т-клетки аттрактирующего хемокина с различными фенотипами атопического дерматита у детей отдельно и в сочетании с другими атопическими коморбидными состояниями (сезонным аллергическим риноконъюнктивитом, круглогодичным аллергическим ринитом, бронхиальной астмой).
Материалы и методы. Основную группу составили 39 пациентов в возрасте от 3 до 18 лет, страдающих атопическим дерматитом отдельно и с коморбидными атопическими состояниями – сезонным аллергическим риноконъюнктивитом, круглогодичным аллергическим ринитом и бронхиальной астмой. Контрольную группу составили 47 детей в возрасте от 3 до 18 лет, без атопии, с заболеваниями желудочно-кишечного тракта. Пациентам обеих групп проводилось определение сывороточных концентраций вышеупомянутых биомаркеров.
Результаты. Были обнаружены достоверно более высокие уровни общего сывороточного иммуноглобулина Е и КТАХ у пациентов с атопией по сравнению с контрольной группой пациентов. Сывороточные уровни ТАРХ не показали достоверных различий между пациентами основной и контрольной групп; тем не менее обнаружена достоверная прямая взаимосвязь со степенью тяжести фенотипов атопического дерматита отдельно и в сочетании с другими атопическими коморбидностями в целом и с клиническим индексом «scoring atopic dermatitis» в частности. Также имелись достоверные обратные ассоциации с возрастом у пациентов основной и контрольной групп. Общий сывороточный иммуноглобулин Е и КТАХ имели достоверные прямые ассоциации со всеми исследованными фенотипами атопического дерматита. Существует сильная перспектива сочетания сывороточного общего IgE, ТАРХ и КТАХ в качестве эффективной панели биомаркеров для оценки интенсивности воспаления при различных фенотипах атопического дерматита.
Выводы. Комбинированное использование общего сывороточного иммуноглобулина Е, тимусом и активацией регулируемого хемокина и кожного Т-клеточного аттрактирующего хемокина представляет собой новую перспективную хемокиновую панель для оценки степени тяжести у детей, страдающих различными фенотипами атопического дерматита отдельно и в сочетании с коморбидными атопическими заболеваниями.
Ключевые слова: атопический дерматит, дети, фенотипы, взаимосвязь, биомаркеры, общий иммуноглобулин Е, тимусом и активацией регулируемый хемокин, кожный Т-клетки аттрактирующий хемокин.

■ INTRODUCTION

Atopic dermatitis (AD) is the chronic skin disease initially manifesting in the infant and pre-school age. Within it`s course chronology it can be followed

by other atopic disorders (AtD): seasonal allergic rhino-conjunctivitis (SARC), perennial allergic rhinitis (PAR) and bronchial asthma (BA). The novel concept of understanding this consequent progression points out at AD as the basic AtD bearing the risk of transforming from a mono-nosology into combined atopic phenotypes: combined with affection of the upper airways (eyes) – SARC and/or PAR and lower airways – BA [1].

The serum levels of total immune globulin E (IgE) alone are often not relevant to evidence the disorder itself and it`s severity degree in particular.

In the past decades there have been being actively studied the novel serum biomarkers (SBM) – the chemokines (CC): thymus and activation regulated chemokine – TARC/CCL17 and cutaneous T-cell attracting chemokine, CTAC/CCL27. The serum levels of the bespoke CC family chemokines are associated with the intensity of AD clinical manifestations of [2].

TARC was discovered in 1996 by Imai et al. [3] and is encoded by the respective gene residing on chromosome 16q13, it serves as the chemo-attractor for T-helpers type 2 cells (Th2). TARC is produced by keratinocytes and dendritic cells in lesional skin and it`s receptors are CC-R4 (CCR4) located on CCR4 positive ($CCR4^+$) $Th_2$ cells. Consequently, the elevation of TARC levels drives the upregulation of the $CCR4^+$ $Th_2$ cells migration into the affected skin zones. Murine models showed that TARC`s expression is elevated within AD by basal keratinocytes as well as by the endothelial cells of the dermis vessels [4]. According to the results of above mentioned meta-analysis there was detected a high association of TARC levels with the skin inflammation severity degree at AD patients.

There is the data to have been emerging during the last 2 two decades about the elevation of TARC levels at the patients with AD compared to the psoriatic patients and the healthy controls [5]. In the aforesaid study serum TARC levels significantly correlated with eosinophilia, «Scoring Atopic Dermatitis» (SCORAD) clinical scale and decreased respectively after treatment following the improvement of the clinical picture of AD. TARC is one of the important chemokines (CC) to correlate reliably with AD activity [6], furthermore, in some countries it had been launched as the biomarker to assess the aforesaid [6, 7].

Cutaneous T-cell attracting chemokine (CTACK/CCL27) is a 112-aminoacid long CC ligand, which`s gene resides at 9p13 chromosome region. As it was detected by the Northern blot analysis, it had been being mostly expressed by skin epidermis basal layers cells keratinocytes within AD as it had been previously determined in CTACK pioneer studies [8]. CTACK facilitates inflammation-specific T-cell trafficking by conducting a signal localizing the cutaneous lymphocyte antigen containing T-memory cells involved in atopic inflammation, particularly within AD [9, 10]. It normally does the same T-cell trafficking within the physiologic immune observation. The in vitro models of preceding decades point out at the fact detected that CTACK synthesis is possibly induced by the pro-inflammatory T-helper cytokines [11] – this enhances the after-trafficking residence of T-memory cells in skin epidermis as the pre-inflammation stage before the onset of AD. Serum CTACK concentrations correlate with the disease severity and it`s regression, particularly, under the cyclosporine A treatment, still less strongly collated to serum TARC concentrations [12]. The above mentioned

similarity of both CTACK and TARC effects on the AD course paved the way to the Hijnen D. et al. hypothesis (2003) that these aforesaid chemokines could facilitate consequently the early recruitment and trans-endothelial migration of T-cells mediated by integrins and, respectively, CTACK accomplishing the process of T-cell trafficking by guiding them through to the upper layers of epidermis – the bespoke induces cascade of epidermal keratinocytes apoptosis-spongiosis being the matrix of the AD skin inflammation [11].

The aforesaid studies support the hypothesis of the present study that total serum IgE, TARC and CTACK are the perspective biomarker panel which could be associated separately or together with the AD activity and other patient-related parameters within different AD phenotypes: alone and with comorbid AtD.

■ PURPOSE OF THE STUDY

To determine the associations of combined SBM panel consisting of total IgE, TARC/CCL17 and CTACK/CCL27 within different AD phenotypes in children – alone and with comorbid AtD (SARC, PAR or BA).

■ MATERIALS AND METHODS

We had recruited 86 children into the study: 39 into the main group and 47 into the control group. All the patients had the duly filled in and signed informed consents for examination and tests which was performed by their legal representatives.

The main group (N=39) was composed of patients suffering from AD of different severity degrees (mild, moderate and severe) which had been assessed clinically by using the SCORAD scale (<20 points – mild degree, 20–40 points – moderate degree, >40 points – severe degree). These patients were recruited at the clinical base of the Department of pediatrics 1 and medical genetics of SE «Dnipro medical academy of Health Ministry of Ukraine», in-patient and counseling-diagnostic departments of the Allergy Centre of MNCE «The emergency medicine hospital of the Dnipro City Council». Inclusion criteria were as follows: age from 3 to 18 years old, the officially established diagnosis of AD alone or combined with other AtD. Exclusion criteria comprised age below 3 or above 18 years old, absence of skin AD specific clinical signs, 0 points by SCORAD scale, officially established diagnosis of the gastro-intestinal tract (GIT) disorders (functional dyspepsia, gastro-esophageal reflux disease (GERD), gastritis, peptic ulcer, functional biliary disorders).

The control group (N=47) was composed of patients, suffering from GIT disorders: functional dyspepsia, chronic gastritis, GERD, functional biliary disorders. Inclusion criteria comprised age from 3 to 18 years old, officially established diagnosis of the aforesaid GIT disorders, no clinical signs of either AD or AtD. Exclusion criteria comprised age below 3 or above 18 years old, any clinical signs of AD or AtD. These patients were recruited at the premises of pediatric gastroenterology department of the MI «City clinical hospital No. 1» of Dnipro city council.

The study presented was performed according to the Declaration of Helsinki (last amendment – 64th WMA General Assembly, Fortaleza, Brazil, October 2013), and all the methods of study and procedures have been approved by the local ethics committee of the SI «Dnipropetrovsk medical

academy of HM of Ukraine»: chairperson – V.V. Koldunov, protocol No. 2 , as of February, 10-th, 2016.

Both the patients of the main and control groups were tested for serum levels of total IgE, TARC and CTACK by taking the venous blood samples fasting. The samples were then duly analyzed in the certified laboratory of «Diagnostic center of the «Medical academy» Ltd using the IgE Elecsys 2010 Immunoassay (serial number 04827031), Human TARC ELISA Kit (ELH-TARC, Lot 013018 0236) and Human CTACK ElisaA Kit (ELH-CTACK, Lot 013018 0311).

To assess the statistical significance of relative values` differences, we applied the Pearson's chi-squared test ($\chi^2$) and Fischer`s exact test, two-tailed (FET, for small cohorts, n<5). The verification of the quantitative characteristics distribution law was performed with Shapiro-Wilk and Kolmogorov-Smirnov test (one-sample), along with Lilliefors test. The mean values are represented as arithmetic means (with 95% confidence intervals (CI)) or medians (low quartile (LQ); higher quartile (HQ)). The statistical significance of the obtained differences was assessed by the Student and Mann-Whitney tests. The direction and strength of obtained associations were evaluated by the application of Spearman rank order correlation coefficient (r_s). All the statistical values were validated by $p<0.05$ critical point. The statistical works had been performed using the Statistica v.6.1 package (Statsoft Inc., USA, license No. AGAR909E415822FA).

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

■ RESULTS

Age and gender distribution. We had obtained the statistically comparable gender distribution of the patients in the main and control groups (table 1).

The data surveilled above depicts a slight prevalence (<10%) of male patients over female ones related to AD phenotypes, still the aforesaid data emerged to be non-significant statistically ($\chi^2=0.72$, $p>0.05$).

The age distribution analysis had showed higher AD incidence in the main group within age cohorts of 4 to 6 and 7 to 11 years old – most frequently children get sick with AD and it`s phenotypes from 7 to 11 years old; in the control group the most of GIT disorders cases had been detected within age cohorts 7 to 11 and 12 to 18 years old – the highest incidence have been detected among children aged 12 to 18 years old (table 2).

Table 1
The gender distribution in the main and control groups

Gender	Main group		Control group		Statistical significance
	N	%	N	%	
Male	21	53.8	21	44.7	p>0.05*
Female	18	46.2	26	55.3	
Total	39	100.0	47	100.0	

Note: * verified by Pearson χ^2 test.

Table 2
The age distribution in the main and control groups

Age (years)	Main group		Control group		Statistical significance
	N	%	N	%	
0–3	2	5.1	1	2.1	p>0.05**
4–6	13	33.4	8	17.0	p>0.05*
7–11	19	48.7	16	34.1	p>0.05*
12–18	5	12.8	22	46.8	p<0.001*
Total	39	100.0	47	100.00	

Notes: * verified by Pearson χ^2 test; ** verified by FET, two-tailed test.

And there had been revealed the significant differences (χ^2=11.43, p<0.001) between the cohort of children aged 12 to 18 years old of the main and control group.

Data described in the table III depicts the mean figures of the age, TARC and CTACK serum concentrations at the patients of the overall main (phenotypes AD alone and AD combined with comorbid AtD) and control groups.

It emerges from the data above that the mean age in years as of AD patients is lower compared to the GIT patients (7.8 to 10.9) evidencing the hypothesis that AD starts earlier in the childhood than GIT disorders. Median serum level of IgE total was significantly 21.9 fold higher in the main group in comparison with the control group which evidences allergic atopic inflammation within AD patients. The data on TARC median serum concentrations did not reveal any significant differences between the main and control groups, therefore mean serum TARC concentrations were 1.1 fold higher in AD patients than those of GIT patients. Median serum level of CTACK was significantly detected 1.3 fold higher in the main group than in the control one which evidences the specificity of CCL-27 as a biomarker for AD in children.

Analyzing the parameters of the age, gender, SCORAD scale as well as TARC and CTACK within patients of the general main and control groups there had been detected the multiple significant associations: age-clinical, age-biomarker and biomarker-clinical within both the groups separately and compared to each other (tables 4 and 5).

Table 3
Age and serum biomarkers in patients of the main and control groups

Values	Main group	Control group	Statistical significance
Age, years; mean value (95% CI)	7.8 (6.7; 8.9)	10.9 (9.7; 12.10)	p<0.001*
IgE Total, IU/ml; median (LQ; HQ)	679.6 (212.2; 1363.0)	31.1 (14.0; 130.2)	p<0.001**
TARC, pg/ml; median (LQ; HQ)	613.8 (390.0; 806.9)	550.6 (415.7; 765.8)	p>0.05**
CTACK, pg/ml; median (LQ; HQ)	4403.6 (3726.2; 5148.7)	3495.9 (3197.8; 4186.8)	p<0.001**

Notes: * verified by Student test; ** verified by Mann – Whitney test.

Table 4
The age-related associations in patients of the main and control groups

Associations: main group	**Number of cases**	**Spearman, r_s**	**p-level**
Age with AD with comorbid AtD	39	0.354	p<0.05
Age with female gender	39	–0.347	p<0.05
Age with serum TARC, pg/ml	39	–0.437	p<0.01
Associations: control group	**Number of cases**	**Spearman, r_s**	**p-level**
Age with serum CTACK, pg/ml	47	–0.347	p<0.05
Age with serum TARC, pg/ml	47	–0.507	p<0.001
Correlations: main and control groups	**Number of cases**	**Spearman, r_s**	**p-level**
Age with AD patients	86	–0.379	p<0.001

The data from table IV points out that atopic patients are significantly older within AD combined with other AtD comorbidities compared to AD alone phenotype (r_s=0.354, p<0.05) and that female AD patients are younger compared to male ones (r_s=–0.347, p<0.05). Age progression had a significant indirect association with serum TARC level decrease at atopic patients of all the AD phenotypes in the main group (r_s=–0.437, p<0.01) and a significant indirect association with the serum TARC and CTACK concentrations at non-atopic patients of the control group (respectively: r_s=–0.347, p<0.05, r_s=–0.507, p<0.001), fig. 1)).

Finally, the patients of overall AD phenotype were detected significantly younger compared to non-atopic patients of the control group (r_s=–0.379, p<0.001; table 4).

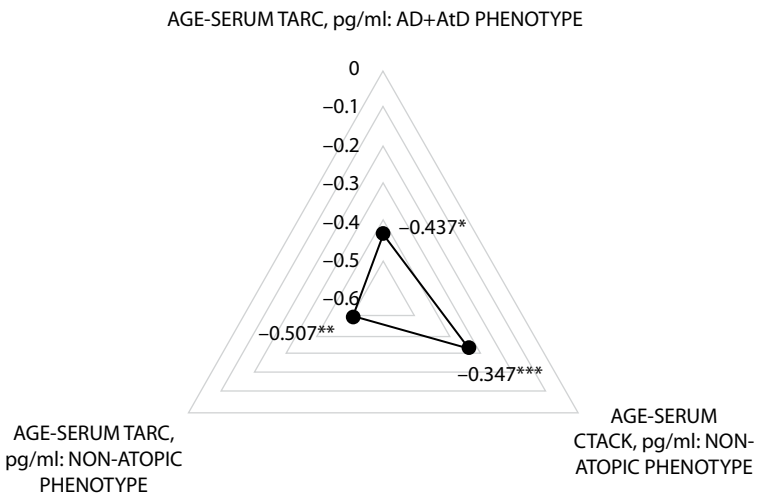

Fig. 1. Serum TARC and CTACK associations with age in patients of all the atopic phenotypes and non-atopic patients

Table 5
The total IgE, TARC and CTACK associations related to clinical manifestations in patients of the main and control groups

Association: main group	**Number of cases**	**Spearman, r_s**	**p-level**
Scorad with serum TARC, pg/ml	39	0.630	p<0.001
Serum TARC, pg/ml with severe AD	39	0.290	p=0.073
Ige total, iu/ml with AD with comorbid AtD	39	0.516	p<0.001
Associations: main with control group	**Number of cases**	**Spearman, r_s**	**p-level**
Ige total, iu/ml with AD patients	86	0.614	p<0.001
Serum CTACK, pg/ml with AD patients	86	0.406	p<0.001

Table V data shows the significant medium positive association as of SCORAD index with serum TARC level (r_s=0.630 respectively, p<0.001). There was detected the trending to significance direct association of serum TARC level elevation within the severe AD clinical degree (r_s=0.290, p=0.073). Along with that, there had been determined direct significant association of AD with comorbid AtD phenotype patients with total serum IgE levels (r_s=0.516, p<0.001). The final comparison of the main and control groups had yielded direct significant associations at the atopic patients of both AD alone and AD with comorbid AtD phenotypes with serum total IgE total and CTACK levels (respectively, r_s=0.614 and r_s=0.406, p<0.001) compared to the non-atopics of the GIT cohort (fig. 2).

■ DISCUSSION

Gender distribution among the main and control groups (table 1) supports the hypothesis that male gender patients are more vulnerable for AtD than female, particularly in toddler and adolescent age.

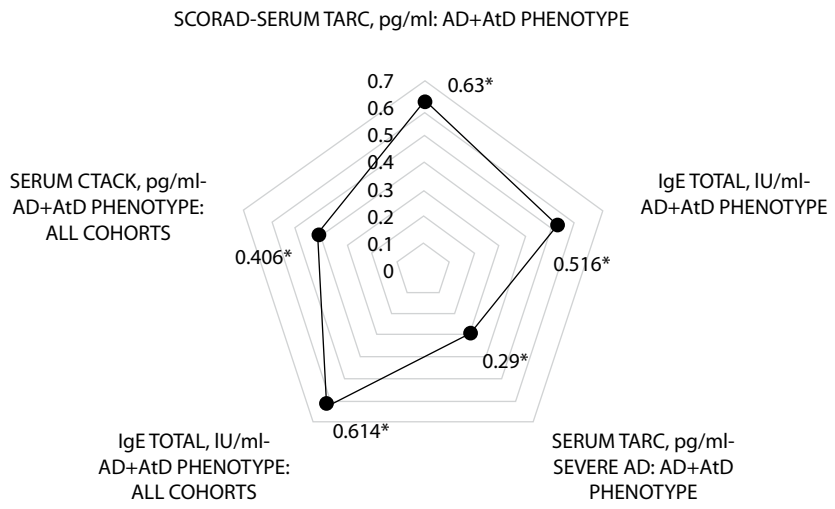

Fig. 2. Serum total IgE, TARC and CTACK associations with clinical manifestations in patients with all the atopic phenotypes and non-atopic patients

The data had been obtained evidencing the significant negative associations of serum TARC and CTACK concentrations with age: atopic patients had the decrease of TARC within getting older (r_s=–0.437, p<0.01) as well as the control group non-atopics had a decrease of both mentioned biomarkers within the age progression (r_s=–0.347, p<0.05 and r_s=–0.507, p<0.001 respectively).

The prototype studies [3] which have focused on the age-related TARC associations comply with this study in a significant decrease of TARC mean concentrations from the infancy to adolescent age. Thus, Y. Kataoka of the bespoke study points out at monitoring serum TARC level as the effective tool to evaluate initial AD activity and it`s treatment efficacy; and managing the serum TARC provides preventing further food allergies and improves AD prognosis within infants. Still, in our study the mean figures of TARC reached 688.1 (LQ 437.9; HQ 820.8) pg/ml and 473.7 (LQ 390.0; HQ 733.4) pg/ml within the AD alone phenotype and AD combined with other AtD phenotype respectively, the aforementioned data being statistically non-significant (p<0.05). This falls out of the Y. Kataoka`s data of normal serum TARC figures <743 pg/ml in children aged 2–15 years old. These discrepancies points at the possible heterogeneity and racial differences among these two studies compared; hence, there is a need for further multi-center research with collating more homogenous patients` cohorts to detect the population-backed TARC differences among the pediatric AD patients.

In present study there was detected that serum total IgE and CTACK concentrations in patients suffering AD combined with other AtD phenotype had been significantly higher than those of non-atopic patients of the control group. Still, not compiling with Machura et al. study on serum TARC and CTACK concentrations in children with AD allergic asthma and urticaria [2], there was not detected any significant difference within the serum TARC concentration between atopic patients suffering BA as one of the components of AD with comorbid AtD phenotype and the non-atopic controls not suffering atopy (respectively 613.8 (390.0; 806.9) pg/ml to 550.6 (415.7; 765.8), p>0.05). The cause of it is due to that study presented had involved patients into the main group suffering the atopic BA obligatorily with AD as the phenotype-setting disorder, and Machura et al. had recruited separate cohorts into the main group consisting of AD, BA and urticaria patients. Secondly, the control group in our study involved GIT disorders, in the bespoke prototype study the healthy non-atopic controls. Similarity of both the studies focuses on the significant association with the TARC serum levels and AD severity degree (assessed by SCORAD index in presented study). The above provided data points out at the need of the further studies in Ukraine with the recruitment of patients suffering separate atopic phenotypes – AD, SARC/PAR and BA alone to more precisely detect the associations of serum TARC and CTACK concentrations and compare them with the results of similar studies abroad. This will allow to finally verify and launch TARC and CTACK as the new chemokine biomarker panel for assessing the AD severity degrees.

In study presented there were detected the following significant associations of studied biomarkers with clinical features of atopic and non-atopic patients: a positive significant TARC/CCL17 with SCORAD (r_s=0.630, p<0.001) within AD combined with other AtD phenotype, trending to significance TARC/CCL17 with AD severity degree (r_s=0.290, p=0.073) in

the main group. All this complies to some extent with Thijs J. et al. (2015) meta-analysis stating TARC as the most reliable biomarker to appraise the severity of AD, and CTACK (CCL-27) being just an additional one requiring additional research [7]. Therefore, the non-significant difference ($p>0.05$) of the serum TARC levels between the atopic patients of the overall main group (phenotypes AD alone and AD combined with other AtD) and non-atopic patients of the control group (GIT phenotype) points out at the necessity of novel studies within larger patients cohorts.

The significant and comparable decrease of serum TARC with age progression at patients of both the main and control groups ($r_s=-0.437$, $p<0.01$ and $r_s=-0.507$, $p<0.001$) suggests a need of a clarifying the role of the mentioned chemokine biomarker in the pathophysiology not just of AD and it`s different phenotypes, but as well the GIT disorders. The hypothesis to be detected is the specific values of TARC for each the age group for both atopic and non-atopic children: infants (0–2 years old), pre-school toddlers (3–6 years old), young school toddlers (7–11 years old) and senior school adolescents (12–18 years old). The same applies to CTACK significant age-related decrease within non-atopic GIT patients – it`s age-specific values should be detected along with TARC in forthcoming studies.

The bespoke data ambiguity of the present study conducted and it`s prototypes to have studied TARC and CTACK still suggest their strong perspective in combination with serum total IgE as the effective biomarker panel for assessing the nature and intensity of skin inflammation. This will yield a more effective control over clinical manifestations of AD different phenotypes. On one hand, it will allow to detect sub-clinical, non-manifesting progression of AD alone into the it`s phenotypes with other atopic comorbidities – seasonal allergic rhino-conjunctivitis, perennial allergic rhinitis, bronchial asthma. On the other hand, it will enable the physicians to prescribe the more personalized treatment which will prevent such the progression, improve AD long-term prognosis and elevate the overall patients` quality of life. All the above mentioned requires further studies within more homogenous patient cohorts.

■ CONCLUSIONS

Total serum IgE concentration is significantly associated with different AD phenotypes, stronger with AD and comorbid AtD than with AD alone phenotype.

The elevation of the TARC/CCL17 serum concentration is significantly associated with SCORAD level in patients of all the AD phenotypes.

The elevation of the CTACK/CCL27 serum concentration is significantly associated with AD in patients of all the AD phenotypes.

Decrease of the TARC/CCL17 and CTACK/CCL27 serum concentrations is significantly associated with the age progression among non-atopic patients.

Combined detection of serum total IgE along with TARC/CCL17 and CTACK/CCL27 is the novel perspective chemokine panel for assessing the AD severity degree in patients suffering the phenotypes of AD alone and AD with comorbid AtD.

The authors declare no conflict of interests.

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