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THE ROLE OF CUTANEOUS T-CELL ATTRACTING CHEMOKINE IN THE DEVELOPMENT OF DIFFERENT PHENOTYPES OF ATOPIC DERMATITIS IN CHILDREN

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Ключевые слова: *атопический дерматит, дети, фенотипы, риск, кутанный Т-клеточный атрактирующий хемокин*

Abstract. The role of cutaneous T-cell attracting chemokine in the development of different phenotypes of atopic dermatitis in children. Dytiatkovsky V.O., Abaturov O.Є., Naumenko N.V., Alifirenko O.O., Filatova I.A., Taran S.M. *The goal of this study was to detect the risk of developing different atopic dermatitis (AD) phenotypes in children (isolated or combined with other comorbid atopic diseases (AtD)) depending on serum concentrations of cutaneous T-cell attracting chemokine (CTACK)/CCL27. The main group comprised 39 children aged 3 to 18 years old suffering from different AD phenotypes – isolated (18 patients) and combined with comorbid AtD – AR/ARC and/or bronchial asthma (21 patients). The control group comprised 47 children aged 3 to 18 years old, suffering from diseases of the gastrointestinal tract (GIT). Serum CTACK/CCL 27 concentrations were detected in all children. In the full main group, the average level of CTACK/CCL27 was significantly higher compared to the patients of the control*

group: 4403.6 pg/ml (95% CI: 3726.2; 5148.7, p<0.001) and 3495.9 pg/ml (95% CI: 3197.8; 4186.8, p<0.001), respectively. Mean serum CTACK/CCL27 levels in patients of the main group with different AD phenotypes were higher than those in the completel main group: with isolated AD – 4549.4 pg/ml (LQ; HQ: 3923.5; 5175.2, p<0.05), with AD associated with other AtD – 5116.6 pg/ml (LQ, HQ: 4062.8; 6170.5, p<0.05). In phenotypes of overall and isolated AD, the cut-off value of serum CTACK/ CCL27 is 3586.5 pg/ml (76.9% and 77.8%, respectively, and 38.3% - in the control grroup). The risk of development at this concentration is 5.37 (95% CI: 2.05; 14.07, p<0.001) for the total AD phenotype and 5.64 (95% 1.56; 20.32, p<0.05) for the isolated AD phenotype. In AD phenotype combined with comorbid AtD, the cut-off value of serum CTACK/CCL27 is 4308.8 pg/ml (66.7% of the main and 21.3% - in the control group). The risk of developing this AD phenotype at this concentration is 7.40 (95% CI: 2.30; 23.76, p<0.001). Serum CTACK/CCL27 levels are the reliable biomarker of the risk for developing different AD phenotypes in children. In the serum level of CTACK/CCL27=3658.5 pg/ml, the significant risk of developing total AD phenotype is 5.37, and isolated – AD=5.64. In the serum concentration of CTACK/CCL27=4308.8 pg/ml, the significant risk of developing AD phenotype combined with comorbid AtD is 7.40.

Реферат. Роль кутанного Т-клеточного атрактирующего хемокина в развитии разных фенотипов атопического дерматита у детей. Дитятковский В.А., Абатуров А.Е., Науменко Н.В., Алифиренко О.А., Филатова И.А., Таран С.М. *Целью данного исследования было изучение риска развития разных фенотипов атопического дерматита (АД) у детей (изолированного или в сочетании с другими коморбидными атопическими заболеваниями (АЗ)) в зависимости от сывороточных концентраций кутанного Т-клеточного атрактирующего хемокина (CTACK)/CCL27. В основную группу были набраны 39 детей в возрасте от 3 до 18 лет, больных разными фенотипами АД – изолированным (18 пациентов) и в сочетании с коморбидными АЗ АР/АРК и/или БА (21 пациент). В контрольную группу были набраны 47 детей в возрасте от 3 до 18 лет, больных заболеваниями желудочно-кишечного тракта (ЖКТ). Всем детям было проведено определение сывороточных концентраций CTACK/CCL27 в крови. В полной основной группе средний уровень CTACK/CCL27 был достоверно выше по сравнению с больными контрольной группы: 4403,6 пг/мл (95% ДИ: 3726,2; 5148,7, p<0,001) и 3495,9 пг/мл (95% ДИ: 3197,8; 4186,8, p<0,001) соответственно. Средние сывороточные уровни CTACK/CCL27 у больных основной группы с различными фенотипами были выше таковых в полной основной группе: с изолированным АД – 4549.4 (НК; ВК: 3923,5; 5175,2, p<0,05), с АД, сочетанным с коморбидными АЗ – 5116,6 (НК, ВК: 4062,8; 6170,5, p<0,05). При фенотипах общего и изолированного АД пороговое значение сывороточного CTACK/CCL27 равно 3586,5 пг/мл (76,9% и 77,8% соответственно и 38,3% в контрольной группе). Риск развития при этой концентрации равен 5,37 (95% ДИ: 2,05; 14,07, p<0,001) для общего фенотипа АД и 5,64 (95% ДИ: 1,56; 20,32, p<0,05) для изолированного фенотипа АД соответственно. При фенотипе АД, сочетанного с коморбидными АЗ, пороговое значение сывороточного CTACK/CCL27 равно 4308,8 пг/мл (66,7% в основной и 21,3% в контрольной группе). Риск развития данного фенотипа АД равен 7,40 (95% ДИ: 2,30; 23,76, p<0,001). Уровень концентрации CTACK/CCL27 в сыворотке крови является достоверным биомаркером риска развития различных фенотипов АД у детей. При сывороточной концентрации CTACK/CCL27 = 3658,5 пг/мл достоверный риск развития общего фенотипа АД равен 5,37, а изолированного АД=5,64. При сывороточной концентрации CTACK/CCL27 =4308,8 пг/мл достоверный риск развития фенотипа АД, сочетанного с коморбидными АЗ, равен 7,40.*

One of the most common diseases of childhood is atopic dermatitis (AD) – it is the most common allergic disease of childhood [3]. It affects up to 25% of the child population [9]. It is well known that early effective therapeutic intervention can stop the progression of AD into severe form with diffuse lesions of the skin of the torso and prevent the development of the so-called "atopic march" (AM) – the addition of other atopic diseases (AtD): allergic rhinitis/rhinoconjunctivitis (AR/ARC) and bronchial asthma (BA). In recent years, there has been developing the hypothesis of AM as an oversimplified approach to understanding the mechanisms of atopy development, which does not take into account all the genetic, ecological and biochemical factors of its development. Therefore, D.C.M. Belgrave et al. proposed an approach to AD as a primary AtD, which over time is combined with respiratory allergy (AR/ARC and/or BA) and forms individual clinical profiles or phenotypes, which begin with skin lesions and migrate to the mucous membranes of the eyes, upper, and then the lower respiratory tract [3]. Based on these assumptions, we divided the BP into two main clinical phenotypes – without respiratory allergies in the form of AR/ ARC and/or BA (AD isolated) and in combination with any of the above atopic nosologies (AD combined with other AtD) [2].

In this case, effective treatment is always based on understanding the mechanisms of pathogenesis of the disease. In the case of AD, particularly in children, this is a complex and unresolved issue, given the many genetic, immunological, biochemical and environmental factors involved in the development of AD. And if a burdened family history of bronchial asthma, male gender, early onset and severe

AD in combination with polyvalent food sensitization are already known as risk factors for AM [13], the group of serum-paraclinical markers known at this time is insufficient to understand and control the severity and course of AD in children. Thus, elevated levels of total immunoglobulin E (IgE) are an important but not pathognomonic factor in the diagnosis of AD – its routine measurement is not recommended for all patients with the strength of evidence A [9]. New views on the pathogenesis of AD indicate a major role of T-helpers type 2 (Th2), which are activated by the interaction of antigens or metals with damaged skin in the development of allergic inflammation in the skin, with total IgE levels increase by no more than in 20% of patients [11]. The author of the above study suggests that the synthesis of IgE by Th2 cells is a secondary phenomenon, because some patients with severe AD have elevated levels of total IgE, while its increase was recorded in non-atopic conditions (parasitic invasions, autoimmune conditions, etc.).

In the realization of the cascade of mechanisms of allergic inflammation in AD, one of the leading roles belongs to chemokines (CK) – biological molecules that direct the activity of T cells located in the skin, and in particular Th2 cells. Thus, the most studied among CK is thymus- and activation-regulated chemokine (CCL17), which is produced by skin keratinocytes and stimulates Th2 cells, which, in turn, correlates with AD severity, IgE levels and eosinophilia in the blood [8, 12]. Meta-analysis by Thijs J. et al. [4] identified CK, which may be useful in understanding complex caskades of inflammation in AD – cutaneous T-cell attracting chemokine (CTACK)/CCL27. It attracts Th-22-lymphocytes that produce interleukin-22, which inhibits the differentiation of epidermal cells and thus increases damage to the skin barrier as one of the main mechanisms of pathogenesis of AD [12, 14]. In the beginning of the CTACK/CCL27 study, the association of CTACK/CCL 27 levels and the severity of AD is indicated, as well as a significant decrease in its serum concentrations with age [10]. Studies in recent years indicate significant differences in the concentrations of CTACK/CCL27 in the stratum corneum of the skin of AD patients in the phase of exacerbation, remission and skin of healthy people [6]. Thus, CTACK/CCL27 concentrations in patients in the exacerbation phase of AD were significantly 3 times higher than in AD patients in the remission phase.

At the same time in Ukraine there are currently no studies on the levels of serum concentrations of CTACK/CCL27 in children with AD – both in terms of associations with severity and prognostic risk of developing different phenotypes of AD – isolated or combined with other AtD.

Therefore, the aim of this study was to examine the serum concentrations of CTACK/CCL27 in children with AD to establish associations with its various forms (isolated or in combination with seasonal ARC, and/or perennial AR, and/or BA).

MATERIALS AND METHODS OF RESEARCH

There were studied 86 children. The main group included 39 children with different phenotypes of AD (isolated and in combination with other AtD (AR/ARC and/or BA). Inclusion criteria in this group: age 3-18 years, established diagnosis of AD in the above phenotypes. Exclusion criteria: age before 3 or over 18 years, absence of clinical AtD, confirmed diagnosis of diseases of the gastrointestinal tract (GIT). Recruitment to the group was carried out at the Department of Pediatrics 1 and Medical Genetics of the Dnipo State Medical University, consultative-diagnostic and inpatient departments of the Allergy Center MCE "Clinical Ambulance Hospital" of the Dnipro City Council.

The control group consisted of 47 children with gastrointestinal pathology (functional dyspepsia, chronic gastritis, gastroesophageal reflux disease, functional disorders of the biliary system). Patients in the control group had no clinical signs of AtD. Inclusion criteria in the control group: age 3-18 years, confirmed diagnosis of gastrointestinal diseases, the absence of clinical manifestations of AtD. Exclusion criteria age younger than 3 or older than 18 years, confirmed diagnosis of AtD. Recruitment to the group was carried out in the Department of Gastroenterology of the City Clinical Hospital No. 9 of the Dnipro City Council".

Clinical determination of AD severity in patients of the main group was performed using the index "Scoring atopic dermatitis" (SCORAD) (Order of the Ministry of Health of Ukraine No. 670 from 04.07.2016). Determination of serum concentrations of CTACK/CCL27 in patients of the main and control groups in venous blood samples was performed in the laboratory of the Diagnostic Center of LLC "Pharmacies of the Medical Academy" using certified diagnostic reagents Human CTACK ELISA Kit (ELH-TARC, serial No. 013018 0236).

Patients' rights were respected in accordance with the Declaration of Helsinki (as amended on 10th of October 2013, adopted by the 64th General Assembly, Fortaleza, Brazil). The Commission on Biomedical Ethics of SE "DMA" approved the proposed research methods (Minutes No. 7 of 28.10.2020). Parents of all children involved in the

study signed informed consents to diagnostic procedures and personal data processing.

Statistical analysis and determination of the reliability of the difference between the relative values of the obtained results was performed using the Pearson Chi-Ssquared test ($\chi 2$); for samples > 5 patients) and Fisher's exact double test (FET) for samples < 5 patients). The average values are presented in the form of medians (lower quartile (LQ), upper quartile (UQ)). CTACK/CCL27 associations and their parameters were measured using the Spearman correlation coefficient (*r)*. Verification of the law of normality of data distribution was carried out using the criteria of Kolmogorov-Smirnov (as adjusted by Liliefors) and Shapiro-Wilk. To determine the risk of developing AD in different phenotypes, logistic regression analysis was used with the calculation of the odds ratio (OR) and 95% confidence interval (95% CI). CTACK/CCL 27 concentration cut-off values were calculated by ROC analysis (receiver operator characteristic plot). The criterion $p<0.05$ was taken as the level of statistical reliability.

The above statistical calculations were performed on the licensed software Statistica v.6.1 (Statsoft Inc., USA, licensed No. AGAR909E415822FA, [1]).

RESULTS AND DISCUSSION

When comparing the gender composition of the main and control groups the following indicators were defined: in the main group, there were 18 or 46.15% girls, and 21 or 53.85% boys of the total; in the control group, girls – 26 or 55.32%, boys – 21 or 44.68% of the total. However, these indicators did not reveal a statistically significant difference between them ($p>0.05$ according to Pearson's $\chi 2$ criterion).

When comparing the age of patients of full main (all phenotypes of AD) and control groups, it was established a significantly lower average age of patients with both isolated AD and AD combined with comorbid AtD, compared with the age of patients with gastrointestinal diseases (Table 1). This confirms the hypothesis of an earlier age of onset of AtD than GIT-pathology.

It also follows from the above table that in the phenotypes of isolated AD and AD combined with comorbid AtD, the age of patients is significantly lower than in patients with GIT diseases. Also, the age of patients with isolated AD is significantly lower than the age of patients with the phenotype of AD combined with comorbid AtD.

Table 1

Comparison of the average age of patients with different AD phenotypes of the main and control group

Groups/cohorts	Number of patients, n	Age: mean, years (-95%; +95% CI)
Full main	**39**	**7.8 (6.7; 8.9)***
Main: AD isolated	**18**	**6.6 (5.2; 7.9)****
Main: AD+comorbid AtD	**21**	**8.9 (7.3; 10.4)****
Control	**47**	**10.9 (9.74; 12.10)***

Notes: * – $p<0.001$ by Student's criterion; ** – $p<0.05$ by Student's criterion.

When measuring serum concentrations of CTACK/CCL 27, results were obtained that indicate significantly higher levels of this CK in children with different phenotypes of AD, compared with patients in the control group without AtD (Table 2). The average values of the full main and control groups are presented in the form of arithmetic means (do not deviate from the normal law of data distribution), and in cohorts of different BP phenotypes – in the form of medians (deviate from the normal law of data distribution).

In determining the associations between CTACK/CCL27 and the parameters of the patients of the main and control groups, direct and inverse associations were established. Thus, in patients of the full main group with all AD phenotypes, a direct reliable association of moderate strength with an increase in the level of this CK ($r=0.406$, $p<0.01$) was determined compared with patients of the control group. In the control group the inverse reliable association of medium strength with increasing age of children was determined ($r= -0.347$, $p<0.05$).

Table 2

Serum levels of CTACK/CCL27 in patients with different AD phenotypes of the main and control gorup

Groups/cohorts	Number of patients, n	CTACK/CCL27, pg/ml
Full main, median (LQ;HQ)	**39**	**4403.6* (3726.2; 5148.7)**
Main: AD isolated, mean (-95%, +95% CI)	**18**	**4549.4** (3923.5; 5175.2)**
Main: AD+comorbid AtD, mean (-95%, +95% CI)	**21**	**5116.6** (4062.8; 6170.5)**
Control, median, (LQ; HQ)	**47**	**3495.9* (3197.8;4186.8)**

Notes: * – p<0.001 by Mann-Whitney criterion; ** – p<0.05 –by Student's criterion.

When using regression analysis, cut-off values of serum concentrations CTACK/CCL27 were obtained, which cause a risk of developing the studied phenotypes of AD. Thus, two values were identified that have significant associations (risk of development) with different phenotypes of AD: 3658.5 pg/ml – specificity = 61.7% (95% CI 46.4-75.5), sensitivity = 77.8 (95% CI 52.4-93.5); 4308.8 pg/ml – specificity = 78.7% (95% CI 64.3-89.3), sensitivity = 66.7 (95% CI 43.0-85.4).

The cut-off value of serum concentration of CTACK/CCL 27 revealed significant associations (OR) with the risk of developing both general and isolated AD phenotypes compared with patients in the control group (Table 3).

Table 3

Distribution and associations of cut-off value of CTACK/CCL27=3658,5 pg/ml among patients with different AD phenotypes of the main and control groups

CTACK/CCL27=3586,5 pg/ml	Full main group, n=39	Main group: isolated AD, n=18	Control group, n=47
Yes, n	**30**	**14**	**18**
Yes, %	**76.9%**	**77.8%**	**38.3%**
No, n	**9**	**4**	**29**
No,%	**23.1%**	**22.2%**	**61.7%**
OR (95% CI)	**5.37* (2.05; 14.07)**	**5.64** (1.56; 20.32)**	

Notes: * – p<0.,001; ** – p<0.05.

Thus, when serum concentrations of CTACK/CCL27 = 3658.5 pg/ml and above are detected in children, the significant risk (OR) of developing AD as a phenotype-forming disease is 5.37, and of isolated AD – 5.64 compared to children in whom the concentration of CTACK/CL27 in the serum is lower than the specified value.

In the study of the cut-off value of CTACK/CCL27 = 4308.8 pg/ml, the one and the values exceeding it were determined in most patients of AD cohort combined with other AtD. This indicator showed a significant risk of developing this phenotype of AD compared with patients in the control group without AtD (Table 4).

The presented study obtained results that indicate a significantly lower age of children with AD of different phenotypes, compared with children in the control group: 7.8, 6.6 and 8.9 years and 10.9 years, respectively. This confirms the own hypothesis about the earlier age of onset of AtD in relation to GIT diseases.

Table 4

Distribution and associations of cut-off value of CTACK/CCL27=4308,8 pg/ml among patients with different AD phenotypes of the main and control group

CTACK/CCL27=4308.8pg/ml	Main group: AD+comorbid AtD, n=18	Control group, n=47
Yes, n	14	10
Yes, %	66.7%	21.3%
No, n	7	37
No,%	33.3%	78.7%
OR (95% CI)	7.40* (2.30; 23.76)	

Note: * – p<0.001.

The scientific novelty of the study lies in the first-ever determined concentrations of CTACK/CCL27 in children with AD. At present, one study of Th-2 CK has been conducted in Ukraine, which identified an increase in TARC/CCL17 levels in children with AD with established sensitization to food allergens [17]. The difference of the original study is the determination of the concentration of CTACK/CCL27 and the risk of developing different phenotypes of AD, regardless of the type of sensitization, due to less-understood the latter in AtD in children.

Significantly higher mean levels of CTACK/CCL 27 in the cohorts of the main group – AD isolated and AD in combination with comorbid AtD – are confirmed by recent studies on increasing serum concentrations of this CK in patients with AtD [16]. But, in contrast to this study, in the above-mentioned study the cohorts of patients of the main group were made up around AD as the basic AtD. In addition, for the first time, the risk (OR) of developing different types of AD was defined, which was not done in the study of E. Machura et al. [16].

In a recent meta-analysis by Y. Renert-Yuval et al. a well-established relationship between CTACK/CCL27 and the severity of AD is indicated, which confirms its important role in the pathogenesis of this disease in children [5]. The strongest correlation of CTACK/CCL27 with SCORAD and tumor necrosis factor alpha (TNF-α) was confirmed in children with hypersensitivity to chicken egg ovalbumin [15].

In general, recent studies of the role of chemokines in the pathogenesis of AD in children have focused on the relationship with severity degree rather than with the risk of disease development [8]. Therefore, there is a prospect of using CTACK/CCL27 as a marker of anti-inflammatory therapy of AD to monitor its effectiveness and review in the absence of clinical improvement in patients. This hypothesis is confirmed by a recent study by E. Roekevisch et al. (2020), which confirmed a significant reduction of this CK in adult patients with severe AD [7].

The presented own study reveals the risk of different phenotypes of AD depending on the serum levels of CTACK CL27, which is its scientific novelty, presented in Tables 3 and 5.

From this we can make assumptions about the marker role of this CK in calculating the risk of AR/ARC and BA. To confirm this hypothesis, studies in separate cohorts of patients with isolated phenotypes of AR/ARC and asthma are required.

CONCLUSION

1. The level of CTACK/CCL27 concentration in blood serum is reliably associated with the development and phenotypic manifestations of atopic dermatitis in children.
2. Serum concentration of CTACK/CCL27 is significantly higher in the phenotype of atopic dermatitis combined with comorbid atopic diseases than in isolated atopic dermatitis.
3. At the level of CTACK/CCL27 in the serum = 3658.5 pg/ml, the significant risk of developing the general phenotype of atopic dermatitis is 5.37, and isolated – 5.64.
4. At the level of CTACK/CCL27 in the serum = 4308.8 pg/ml, the significant risk of developing the phenotype of atopic dermatitis combined with comorbid atopic diseases is equal to 7.40.
5. To finally determine the role of CTACK/CCL27 in the pathogenesis of allergic rhinitis/rhinoconjunctivitis and BA and its associations with different phenotypes of atopic dermatitis, further studies are required in cohorts of patients stratified separately by these nosologies.

Conflict of interest. The authors declare no conflict of interest.

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