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Features of Cytokine Status in Children with Atopic Dermatitis

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The paper presents the results of our investigation of the cytokine status features and contents of soluble form of vascular cellular adhesion molecules in children with atopic dermatitis and atopic dermatitis on the background of undifferentiated connective tissue dysplasia. In atopic dermatitis the content of interleukin-2, interleukin-4, and soluble form of vascular cellular adhesion molecules has been proved to increase by contrast to healthy children. Immunoregulation indices have been noted to increase with severity of atopic dermatitis rise. Analysis of intercorrelation relationships between interleukin-2, interleukin-4, and soluble form of vascular cellular adhesion molecules in the system of cytokines demonstrated that they are in an intricate correlation between themselves and with IgE, and these relationships' intensity and direction depended upon the severity of atopic dermatitis. Concomitant connective tissue dysplasia causes more significant immunoregulation indices deviations in case of severe course of atopic dermatitis.

Keyword: *Atopic dermatitis, children, connective tissue dysplasia, interleukins.*

1. Introduction

According to World Allergy Organization (2011 – 2012) prevalence rate of allergic diseases in the world is rising dramatically [1]. Herein atopic dermatitis (AD) is one of the most common allergic diseases in children. Official statistics show that the prevalence of such a pathology in Ukraine makes up 3-10%. According to the data of epidemical survey the prevalence of AD in children in the USA makes up 17,2%, in Japan – 24%, in European countries – 15,6%, in Russia – 5,2-15,5%, in Ukraine – 3,9%. [2, 3].

Great prevalence and inadequate AD treatment effect in children is associated with the complexity of its pathogenetic mechanisms that are difficult to identify in every case. This is precisely why new high-information methods that will help not only in optimal diagnosis but also in its maximal individualization are searched for [4, 5].

Currently cytokines are thought to play the most important part in regulation of the immune response in AD. In AD pathogenesis the most significant is the conception of Th1/Th2 response with the release of proinflammatory cytokines IL-2 and IL-4 and switching on the immune response to IgE hyperproduction [3, 5]. At the same time a number of cytokines, including IL-4, are known to stimulate expression of vascular cell adhesion molecule (VCAM-1) on the endothelium. These molecules provide adhesion of the immune cells to the endothelium as well as their transmigration from the vessel flow to tissues with an allergic inflammation development. Serum vascular cell adhesion molecule level (sVCAM-1) is thought to be proportional to the level of its fraction expressed on the endothelium [6, 7].

The purpose of this study was to ascertain features of relationship of IL-2, IL-4 and sVCAM-1 in children with different degrees of

AD severity in the presence of underlying connective tissue dysplasia (CTD).

Table 1: Concentration of serum cytokines and vascular cellular adhesion molecules in healthy children and in children with atopic dermatitis depending upon the disease severity and in undifferentiated connective tissue dysplasia (M±m).

AD severity		***Indices***		
		IL-2, pcg/ml	**IL-4, pcg/ml**	***s-VCAM-1, ng/ml***
Mild	I[1] (n=14)	6,88±1,03*	1,84±0,34*	863,14±123,1
	II[2] (n=11)	6,90±1,18*	2,15±0,41*	858,23±105,7
Moderately severe	I [3](n=28)	5,24±1,21	4,29±0,55*	1179,6±128,5*
	II[4] (n=27)	4,35±0,81	4,71±0,33*	1285,45±143,4*
Severe	I[5] (n=18)	8,55±1,14*	5,85±0,47*	1683,50±249,5*
	II [6](n=22)	7,78±1,25*	6,14±0,51*	2451,47±256,2*
Healthy children	n=(20)	3,84±0,29	0,40±0,26	889,3±122,42
p		$p_{3-5}<0,05$ $p_{4-6}<0,05$	$p_{1-5}<0,01$ $p_{2-6}<0,01$ $p_{1-3}<0,05$ $p_{2-4}<0,05$	$p_{1-5}<0,001$;$p_{2-6}<0,001$ $p_{1-3}<0,05$;$p_{2-4}<0,05$ $p_{3-5}<0,05$;$p_{4-6}<0,05$ $p_{5-6}<0,05$

Notes: 1.* – significance of differences between indices of children with AD and healthy children ($p<0,05$)
2. p – significance of differences between patients of Clinical Groups I and II, healthy children and in mild, moderately severe, and severe clinical course of the disease

2. Material and Methods

We investigated 120 children with AD aged from 1 to 18 years in the period of the disease exacerbation. Diagnosis of AD was verified using J.M.Hanifin's and G. Rajkas criteria (1980). Children with AD were divided into two groups: I – 60 children suffering from AD with manifestations of undifferentiated CTD; II – 60 children suffering from AD without manifestations of undifferentiated CTD. On the basis of complications, anamnesis and physical examination we evaluated the intensity of the main clinical symptoms of AD using SCORAD scores and ascertained the severity of the disease clinical course. According to the severity score children with AD were distributed the following way: 14 and 11 children – with mild, 28 and 27 – with moderately severe, 18 and 22 – with severe allergodermathosis correspondingly in clinical groups I and II. 20 apparently health children were controls.

Concentration of IL-2, IL-4 in blood serum was detected using solid-phase enzyme-linked immunosorbent sets: produced by CJSC "Vector Best"; A-8754 and A-8754 and A-8772 (Russia); s-VCAM-1 – produced by Bender Med Systems BMS232.

Statistical data processing was made using arithmetic middling (M) and arithmetic middling mean accuracy m (M±m). To evaluate the intensity and direction of correlation between indices we used pair correlation coefficient (r). Differences between groups were considered to be accurate when $p<0,05$.

3. Results and Discussion

Analysis of IL-2, IL-4, s-VCAM-1 mean levels in children with AD showed their accurate increase by contrast to healthy children. At the same time we didn't find out a great difference in immunoregulation indices in relation to CTD manifestation. Thus, mean level of IL-2 in patients with AD was (6,68±1,23) pcg/ml, IL-4 – (3,57±0,63) pcg/ml, s-VCAM-1 – (1242,21± 216,97) ng/ml vs. (3,84±0,29), (0,40±0,26) and (889,3±122,42) in healthy children, in pursuant to ($p<0,05$) (Table 1). At the same time changes in cytokine system have been noted in children depending upon the severity of AD. Thus, the level of IL-2 I in patients with mild AD was rather high in both groups of patients. It differed from the similar finding in healthy children ($p<0,05$). In severely moderate course of the disease this finding decreased to the level of healthy children, and in children with severe AD it was the highest and, constituting (8,55±1,14) pcg/ml and (7,78±1,25) pcg/ml in groups I and II, was definitely higher than in patients with moderately severe course ($p<0,05$).

Different tendency was observed concerning IL-4 levels. Thus, the level of IL-4 rose with the severity of AD increase and in severe clinical course was greater than in children with mild course in two and a half times ($p<0,01$). At the same time the level of IL-4 was definitely higher in all patients than in healthy children ($p<0,05$).

The content of s-VCAM-1 in mild AD was virtually the same as in healthy children while in moderately severe disease it significantly increased ($p<0,05$). Severe allergodermathosis was characterized by the maximal increase of s-VCAM-1 index. Constituting (1683,50±249,5) and (2451,47±256,2) ng/ml in severe clinical course of AD in patients of group I and group II, accordingly, s-VCAM-1 index was definitely higher that not only the same index in healthy children ($p_N<0,05$), but also those in mild and severe disease ($p<0,05$). At the same time in children with severe AD s-VCAM-1levels were significantly higher than the same indices in children without connective tissue dysplasia manifestations ($p<0,05$).

To investigate intricate relationships in the system of cytokines and their role in IgE-mediate reactions analysis of coefficient correlation has been made. Correlation analysis demonstrated that s-VCAM-1, IL-2, IL-4 and IgE levels in children with AD are in an intricate dynamic correlation, intensity and direction of which depend upon the severity of dermatitis. Thus, in mild AD there were no essential correlations between interleukins and s-VCAM-1, IgE levels had a direct weak correlation relationship with IL-4 ($r = 0,17$) and weak feed-back correlation relationship with s-VCAM-1($r = -0,23$). In moderately severe AD there was a direct weak correlation of s-VCAM-1with IL-4 ($r = 0,29$) and direct moderate – with IL-2 ($r = 0,31$). At the same time moderate feed-back correlation was noted between IgE level and IL-2 ($r = -0,34$) (Table 2). In case of severe allergodermathosis correlations change. Correlation intensity of s-VCAM-1 with IL-2 increased ($r = -0,93$), interrelation of IgE with IL-4 became feed-back ($r = -0,16$). The interrelationship between interleukins was the most intense increasing with the severity of dermatitis and constituting ($r = 0,40$) in mild disease and ($r=0,80$) – in the severe course.

Our investigation demonstrated that activation of cytokine system with simultaneous activation of Th1 and Th2 function is observed in children with AD. Significant increase of IL-4 level was observed even in mild disease increasing progressively with the severity of the disease. Severe AD was characterized by maximal levels of IL-2 and IL-4.

S-VCAM-1 level in mild AD didn't differ from the same index in healthy children but increased greatly in mildly severe and severe AD. All the evidence goes to prove that adhesion molecules are prominent in the development and chronization of allergic inflammation.

Table 2: Intercorrelation relations between middle levels of interleukins, vascular cellular adhesion molecules and IgE in children with a distinct severity of atopic dermatitis (r)

Indices	IgE	s-VCAM-1	IL-2	IL-4
Mild atopic dermatitis				
IgE	X	-0,23	-0,06	0,17
s-VCAM-1	-0,23	X	0,02	-0,07
IL-2	-0,06	-0,02	X	0,45
IL-4	0,17	-0,07	0,45	X
Moderately severe atopic dermatitis				
IgE	X	-0,16	-0,34	0,21
s-VCAM-1	-0,16	X	0,31	0,29
IL-2	-0,34	0,31	X	0,40
IL-4	0,21	0,29	0,40	X
Severe atopic dermatitis				
IgE	X	0,19	-0,23	-0,16
s-VCAM-1	0,19	X	0,39	0,12
IL-2	-0,21	0,39	X	0,80
IL-4	-0,16	0,12	0,80	X

4. Conclusions

1. Intricate relationship of immunoregulation indices is characteristic for AD: there is an activation of cytokines and adhesion molecules providing intercellular cooperation in the process of allergic reaction. Direction and intensity of such an interaction is determined by the severity of allergodermathosis.
2. Relationship between IL-2, IL-4, s-VCAM-1 and IgE may be multidirectional, and increase of their contents is an objective measure for the detection of AD severity and prognosis.
3. Background connective tissue dysplasia contributes to more significant deviations of immunoregulation indices in case of severe AD.

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