PEDIATRICS

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THE ROLE OF VASCULAR INTERCELLULAR ADHESION MOLECULE-1 (SVCAM-1) IN INFLAMMATION DEVELOPMENT ACCOMPANYING BRONCHIAL ASTHMA IN CHILDREN

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Abstract: The goal of the investigation is to evaluate the role of sVCAM-1 in inflammation development in children suffering from bronchial asthma at the period of exacerbations and remission. The study included 91 patients with persistent bronchial asthma at the age of 6 to 17 years. The serum levels of sVCAM-1 was determined with enzyme-linked immunosorbent assay. Intima media complex thickness of common carotid artery was detected applying to the method of Pignolli P. (1986). Clinical investigations of blood were performed according to common methods. Statistic analysis was performed using Statistics packages such as "EXCELL FOR WINDOWS" and "STATISTICA 7.0. FOR WINDOWS". The study of sVCAM-1 level in blood serum of children suffering from BA showed its significant increase in mentioned patients both at the exacerbation and remission periods, and it depends on disease severity; its decrease was reported at remission period. sVCAM-1 was found to directly participate in inflammatory cells adhesion processes (neutrophils, eosinophils, and monocytes) on vascular endothelium with their further migration not only at the period of BA exacerbation but also at remission period. It leads to development of local inflammation and thickening of vascular wall. The present correlations with external respiration function suggest direct participation of sVCAM-1 in development of endothelial dysfunction and severity of BA manifestation.

KeyWords: bronchial asthma, children, inflammation.

INTRODUCTION

Bronchial asthma (BA) is considered to be the most widespread chronic condition among children, and remains a global problem of health protection [4, 9]. Inflammation specific for this pathologic process can be caused by different factors including allergens, viruses, physical activity, etc., and results from changes in immune system including cellular, humoral mechanisms, and resembles a complex process which results in immune balance disorder [1,2]. BA pathogenesis is influenced by IgE-mediated allergic reactions which also result from changes in immunoregulation system [5]. At the time of inflammatory reaction development endothelium, thrombocytes, leukocytes, coagulation plasma system, and complement system always interact [3, 7,10].

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Vascular remodeling molecular mechanisms of which are complex and underinvestigated plays a significant role in pathogenesis of chronic process in respiratory tract [4, 8]. Endothelium plays many important functions including barrier and transport ones, synthesis of proteins and vasoactive substances, takes part in angiogenesis, blood coagulation processes, regulates vascular tone and immunoinflammatory reactions [11, 14]. Moreover, endothelial cells express a significant number of biologically active substances (anti-inflammatory cytokines, chemokines and enzymes, anticoagulants, vasoconstrictors and vasodilators, and also adhesion molecules) which directly take part in inflammatory process, and not only initiate but also support it [12, 13, 14]. Inflammation leads to activation of endothelial cells which are participants and regulators of inflammatory process expressing intercellular adhesion molecules [12]. Hereafter it causes the increase of vascular penetration [12, 13].

It appears that the perspectives of further scien-

tific search for investigation of BA development mechanisms, formation and progressing can include extended detection of vascular and endothelial factors in genesis of chronic inflammatory process of bronchopulmonary system [3].

2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

To evaluate the role of sVCAM-1 in inflammation development in children suffering from bronchial asthma at the period of exacerbations and remission.

2.2 Subjects

`We examined 91 children suffering from persistent BA (50 boys and 41 girls) at the age of 6-17 years at the periods of exacerbations and remission of the disease. The examination was performed at Pulmonology Department of Communal Health Institution "Kharkiv Municipal Children's Clinical Hospital #16". The diagnosis was made taking into account the demands stated in corresponding protocol with BA (order #868 Ministry of Healthcare of Ukraine d.d. 08.10.2013). The research also included examination of 15 apparently healthy children who belonged to control group.

Depending on disease severity children were divided into 3 groups: 1st group – children with light persistent disease course (40); 2nd group – children with moderately severe BA (34); 3rd group – with severely persistent BA (17)

2.3 Methods

The level of sVCAM-1 was detected in blood serum with the help of BenderMedsystems kit (Austria) for sVCAM-1 identification. Clinical investigations of blood were performed according to common methods (В.Е. Предтеченський, 1960), levels of glycoproteins and seromucoids based on unified method (В.В.Меньшиков, 1987). Intima media complex thickness of common carotid artery (IMC CCA) was detected applying duplex sonography in the distal third of the common carotid artery according to the method of Pignolli P. (1986). The function of external respiration was assessed according to the method of computed pneumotachography using "Custo-Vit" apparatus (Germany).

Statistic analysis was performed using Statistics packages such as "EXCELL FOR WINDOWS" and "STATISTICA 7.0. FOR WINDOWS". For sampling methods with allocation different from the normal one median (Me) and interquartile range were defined (Lq – lower quartile; Uq – upper quartile).

While comparing values which were characterized by comparison of more than 2 points Kruskal-Wallis H-test dispersion analysis was applied. Significance point was defined using Bonferonni adjustment. To compare two independent samples non-parametric Mann-Whitney U-test was applied. To compare two dependent samples non-parametric Wilcoxon test was used. The relation between values was assessed by the method of Spearman rank correlation. Significance point was detected taking into account $p<0.05$.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

sVCAM-1 in blood serum depending on disease course severity was assessed (Table 1). It was significantly increased comparing with values of control group children.
After analysis of statistical characteristics of multiple comparison of sVCAM-1 value in blood serum of children suffering from BA it was reported that Kruskal-Wallis H-test was highly significant. It allows confirming that statistical characteristics of different groups significantly differ from one another, and its level depends on patient's belonging to this or that group (that is the disease severity). At the time of sequential comparison of the given value statistically significant increase of its level in blood serum in all people suffering from BA both in exacerbation and remission period was detected. The most expressive changes are identified in children of the 3rd group with severe stage of disease.

Table 1.

Statistical characteristics of sVCAM-1 level in blood serum of children suffering from BA at the period of exacerbation and remission Me (Lq; Uq

Groups of children	sVCAM-1, ng/ml	KW ANOVA by Ranks	MW U Test
Exacerbation period			
1st group (n=34)	990.27 (900.52; 1080.89)	H=67.30, p= 0.0000	p_{1-2}= 0.0000; p_{1-3}= 0.0000; p_{2-3}= 0.0000; p_{c-1}= 0.0000; p_{c-2}= 0.0000; p_{c-3}= 0.0000;
2nd group (n=31)	1280.00 (1100.27; 1380.73)		
3rd group (n=11)	1700.73 (1480.27; 1920.59)		
Control group (n=15)	730.01 (690.63; 790.19)		
Remission period			
1st group (n=40)	885.42 (800.57; 990.47)	H=76.57, p= 0.0000	p_{1-2}= 0.0000; p_{1-3}= 0.0000; p_{2-3}= 0.0000; p_{c-1}= 0.0000; p_{c-2}= 0.0000; p_{c-3}= 0.0000;
2nd group (n=34)	1150.43 (990.37;1280.77)		
3rd group (n=17)	1500.18 (1300.32; 1700.25)		
Control group (n=15)	730.01 (690.63; 790.19)		

The dependency of sVCAM-1 levels expressiveness in blood serum on disease activity is also proven by growing with severity process significant correlation factors (p<0,05) of this value and values of acute inflammation phase including levels of glycoproteins and seromucoid in blood serum: patients of the 1st group were reported to have medium strength correlation between the levels of the given values (r=+0.3492, r=+0.4487, respectively); the given correlation in children of the 2nd group equaled to r=+0,5825 and r=+0,5043, respectively; the patients of the 3rd group were reported to have strong correlation of sVCAM-1 level in blood serum with acute phase values (r=+0,8909 – glycoproteins, r=+0,9151 – seromucoid).

The analysis of sVCAM-1 level in blood serum of children suffering from BA at different disease periods demonstrated that at remission period this value remains higher than regulatory values (p<0,001), however compared with exacerbation period it is significantly reduced in patients of the 1st, 2nd, and 3rd groups (p=0.0000, T=0.00; p=0.0000, T=0.00; p=0.0033, T=0.00, respectively). It can signal about presence of pathologic process even beyond activity, and be an adverse factor in disease course.

While detecting the thickness of IMC CCA, children of the 1st, 2nd and 3rd groups were reported to have significant increase of the given value 0.9(0.8; 1.0) mm; 1.0 (0.9; 1.2) mm; 1.2(1.1; 1.3) mm, respectively, compared with values of control group – 0.6 (0.5; 0.7) mm, p<0.001).

Further statistical processing showed high direct correlation between sVCAM-1 level in blood serum and IMC CCA thickness both at exacerbation period (r=+0.8, p<0.05) and remission period (r=+0.8, p<0.05). Thus, it is possible to admit direct participation of sVCAM-1 in development of inflammatory process in vascular endothelium.

The presence of correlation between sVCAM-1 level in blood serum and IMC CCA thickness with inflammatory cells (leukocytes) in blood at exacerbation and remission periods was analyzed.

Positive correlation relationships of sVCAM-1 level of blood serum and IMC CCA thickness with leukocytes (r=+0.4, p<0.05) and neutrophils (r=+0.3, p<0.05) in children of the 1st group at exacerbation period and significant increase of bonding strength of IMC CCA thickness with neutrophils in patients of the 3rd group (r=+0.7, p<0.05) were detected.

Converse correlation of the given values with lymphocytes in children of the 1st group (r=-0.4, p<0.05) and significant increase of bonding strength of the given correlation in patients of the 3rd group (r=-0.8, p<0.05) was also identified. Analyzing inflammation from the side of tissue infiltration of leukocytes it is necessary to admit that mediators which influence endothelial cells also affect leukocytes, and vise versa. Thus, microvascular endothelial cells at inflammation site are active participants and regulators of inflammatory processes [13]. Moreover, it is necessary to note that children of the 2nd and 3rd groups have positive correlation of sVCAM-1 level of blood serum with eosinophils (r=+0.4, p<0.05 – in patients of the 2nd group and r=+0.6, p<0.05 – in patients of the 3rd group) and negative

correlation – between IMC CCA thickness and monocytes (r=-0.6, p<0.05). The identified changes can be explained by the fact that ß1-integrin which is expressed on leukocytes of some subpopulations provides selective adhesion of monocytes and eosinophils on endothelium and further sVCAM-1 causes their migration and inflammation development [71]. Thus, increased expression of sVCAM-1 by activated endothelium causes recrutization of inflammatory cells and their further transendothelial migration. It can lead to their accumulation in intima and further to thickening of vascular wall.

At remission period patients of the 1st group still have negative correlation of sVCAM-1 level of blood serum and IMC CCA thickness and lymphocytes (r=-0.5, p<0.05), children of the 2nd group have positive correlation between sVCAM-1 level of blood serum with neutrophils (r=+0.7, p<0.05), and patients of 3rd group – negative connection of the given value with monocytes (r=-0.7, p<0.05). Thus, at remission period inflammatory cellular adhesion to endothelium can continue, and it leads to its hypertrophy and further to intima thickening with formation of long-term damages of endothelium adequate functioning.

Significant dependency of external respiration function on sVCAM-1 level is proven by existing correlations (with forced vital capacity - r=-0.5; with forced expiratory volume 1- r=-0.4; with MEF25 - r=-0.5; with MEF50 - r=-0.3; p<0.05) – at the period of exacerbations; and at remission period (with forced vital capacity - r=-0.3; with forced expiratory volume 1- r=-0.5; with MEF75 - r=-0.3; p<0.05). Thus, the higher are levels of sVCAM-1 in blood serum the worse are the values of external respiration function especially those ones which are specific for BA – forced expiratory volume 1, peak expiratory flow rate that is the evidence of adhesion vascular molecule belonging to inflammatory process and external respiration dysfunction in BA.

4 CONCLUSIONS

The study of sVCAM-1 level in blood serum of children suffering from BA showed its significant increase in mentioned patients both at the exacerbation and remission periods, and it depends on disease severity; its decrease was reported at remission period. sVCAM-1 was found to directly participate in inflammatory cells adhesion processes (neutrophils, eosinophils, and monocytes) on vascular endothelium with their further migration not only at the period of BA exacerbation but also at remission period. It leads to development of local inflammation and thickening of vascular wall. The present correlations with external respiration function suggest direct participation of sVCAM-1 in development of endothelial dysfunction and severity of BA manifestation.

Thus, expression of sVCAM-1 by different cells forms pathological process which leads to stable changes in vascular endothelium and is one of the mechanisms of chronic inflammation formation.

REFERENCES

1. Yachnik A., Pobedennaya G. (2005) Mehanizmyi realizatsii hronicheskogo vospaleniya pri bronhialnoy astme i vozmozhnyie podhodyi k lecheniyu [The mechanisms of realization of chronic inflammation in asthma and possible approaches to treatment]. Ukr. pulmonol. zhurn, no 1, pp. 60-63.

2. Budovskaya L. (2012) Mekhanizmy vospaleniya pri sochetanii bronhial'noj astmy i ishemicheskoj bolezni serdca [The mechanisms of inflammation in asthma , and combination of coronary heart disease]. Ukraïns'kij pul'monologichnij zhurnal, no 1, pp. 68-72.

3. Voronina L. (2011) Geneticheskie, biohimicheskie i funkcional'nye markery sostoyaniya vazoregulyaruyushchej funkcii ehndoteliya [The genetic , biochemical , and functional status vazoregulyaruyuschey markers of endothelial function]. Sibirskij medicinskij zhurnal (Irkutsk), no 3(102), pp. 29-31.

4. Alagappan, V. K., de Boer, W. I., Misra, V. K., Mooi, W. J., & Sharma, H. S. (2013). Angiogenesis and vascular remodeling in chronic airway diseases. Cell biochemistry and biophysics, 67(2), 219-234.

5. Balabolkin I., Smirnov I., Bulgakova V., Goryunov A., Lar'kova I. (2006) Sovremennaya koncepciya

patogeneza bronhial'noj astmy u detej [The modern concept of the pathogenesis of asthma in children]. Immunopatologiya, allergologiya, infektologiya, no 1, pp. 26-35.

6. Talaeva T. (2001) Mekhanizmy vzaimodejstviya kletok krovi i sosudistoj stenki v realizacii vospalitel'nogo i immunnogo otvetov [Mechanisms of interaction of blood cells and vascular inflammation and in the implementation of immune responses]. Ukr. revmatol. zhurn, no 3, pp. 5-6.

7. Lysikova M., Val'd M., Masinovski Z. (2016). Mekhanizmy vospalitel'noj reakcii i vozdejstvie na nih s pomoshch'yu proteoliticheskih ehnzimov [The mechanisms of the inflammatory response and their effect on proteoly - ic enzymes]. Zhurnal'Citokiny i vospalenie, no 3, pp 45-48.

8. Su, X., Ren, Y., Yu, N., Kong, L., & Kang, J. (2016). Thymoquinone inhibits inflammation, neoangiogenesis and vascular remodeling in asthma mice. International immunopharmacology, 38, 70-80.

9. Hendaus, M. A., Jomha, F. A., & Ehlayel, M. (2016). Allergic diseases among children: nutritional prevention and intervention. Therapeutics and clinical risk management, 12, 361.

10. Kulinskij V. (2007) Biohimicheskie aspekty vospaleniya [Biochemical aspects of inflammation]. Sibirskij medicinskij zhurnal, no 1, pp. 95-101.

11. Sayner, S. L. (2011). Emerging themes of cAMP regulation of the pulmonary endothelial barrier. American Journal of Physiology-Lung Cellular and Molecular Physiology, 300(5), L667-L678.

12. Yang, X., Chang, Y., & Wei, W. (2016). Endothelial Dysfunction and Inflammation: Immunity in Rheumatoid Arthritis. Mediators of inflammation, 2016.

13. Pober, J. S., & Sessa, W. C. (2007). Evolving functions of endothelial cells in inflammation. Nature Reviews Immunology, 7(10), 803-815.

14. Shevchenko Yu., Astashov P., Matveev S., Gudymovich V. (2011) Endotelij–strukturnaya osnova sistemy krovoobrashcheniya: istoriya problemy [The endothelium - structural basis of the circulatory system : the history of the problem]. Vestn. Nacional'nogo mediko-hirurgicheskogocentra im. N.I. Pirogova, no 6, pp. 9-15.

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