МЕТАЛЛОПРОТЕИНАЗА-9 И ЕЕ РОЛЬ В ПАТОГЕНЕЗЕ АЛЛЕРГИЧЕСКИХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

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Резюме. Металлопротеиназы (ММР) играют значимую роль в механизмах поддержания хронического воспаления и ремоделирования тканей. Изучение изменений концентрации этих ферментов в сыворотке крови у детей с аллергопатологией представляет большой практический и научный интерес.

Цель – изучить роль ММР-9 в патогенезе аллергических заболеваний у детей. 180 детей в возрасте от 1 года до 18 лет прошли комплексное клинико-лабораторное обследование. В это исследование были включены пациенты, страдающие бронхиальной астмой (ВА) (n = 54), атопическим дерматитом (AD) (n = 54) и сочетанием этих патологий (n = 72). Уровни ММР-9 в сыворотке крови определяли методом иммуноферментного анализа с использованием тест-систем Cloud-CloneCorp® (США). Результаты клинических, инструментальных и лабораторных исследований пациентов были соотнесены с данными ИФА-исследования уровня ММР-9 в сыворотке крови.

Анализ полученных данных показал, что среди пациентов с установленным диагнозом «БА» максимальная концентрация этого цитокина была зарегистрирована у детей со среднетяжелым течением заболевания. Проведенный корреляционный анализ показал наличие значимой корреляции между тяжестью БА и уровнем контроля над заболеванием (r = 0,63). Аналогичные данные были получены у пациентов с сочетанием БА и АД. У детей этой группы также наблюдалось значительное повышение уровня ММР-9 в сыворотке крови по сравнению со здоровыми пациентами (p = 0,015). Максимальные показатели были зарегистрированы у пациентов со среднетяжелым течением БА. Концентрация этой матриксной металлопротеиназы в сыворотке крови была несколько выше у детей с поливалентной сенсибилизацией, чем у пациентов с моноаллергической этиологией заболевания (p = 0,272). Показатели ММР-9 у пациентов только с кожными проявлениями атопии были достоверно выше, чем в контрольной группе (p = 0,025). При этом не было никаких различий в зависимости от пола. Было установлено, что максимальные значения ММР-9 были зарегистрированы среди детей с подростковой формой АД.

Полученные нами данные показали, что у всех обследованных нами пациентов наблюдалось значительное повышение уровня ММР-9 в сыворотке крови, что указывает на важную роль этого цитокина в патогенезе аллергических заболеваний у детей.

Ключевые слова: металлопротеиназа-9, бронхиальная астма, атопический дерматит, диагностика, патогенез, дети

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METALLOPROTEINASE 9 AND ITS ROLE IN THE PATHOGENESIS OF ALLERGIC DISEASES IN CHILDREN

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Abstract. Metalloproteinases (MMP) play a significant role in the mechanisms of maintaining chronic inflammation and tissue remodeling. The study of concentration changes in these enzymes in the blood serum of children with allergopathology is of great practical and scientific interest.

Objective: to study the role of MMP-9 in the pathogenesis of allergic diseases in children. 180 children aged from 1 to 18 years passed a comprehensive clinical and laboratory examination. This study included patients suffering from bronchial asthma (BA) (n = 54), atopic dermatitis (AD) (n = 54) and combination of these pathologies (n = 72). Serum levels of MMP9 were determined by enzyme immunoassay using Cloud-CloneCorp® test systems (USA).

The analysis of the obtained data showed that among patients with the established diagnosis of BA, the maximum concentration of this cytokine was registered in children with a moderate course of the disease. The conducted correlation analysis showed the presence of a significant correlation between the severity of asthma and the level of control over the disease (r = 0.63). Similar data was obtained in patients with a combination of BA and AD. In children of this group, there was also a significant increase in serum MMP-9 compared with healthy patients (p = 0.015). The concentration of this matrix metalloproteinase in serum was slightly higher among children with polyvalent sensitization than in patients with monoallergic etiology of the disease (p = 0.272). The values of MMP-9 in patients with only skin manifestations of atopy were significantly higher than in the control group (p = 0.025).

The data we obtained showed that all the patients we examined had a significant increase in the level of MMP-9 in the blood serum, which indicates an important role of this cytokine in the pathogenesis of allergic diseases in children.

Keywords: metalloproteinase 9, bronchial asthma, atopic dermatitis, diagnostic, pathogenesis, children

Introduction

Allergy is a specific immune reaction of the body to an allergen which is accompanied by the development of chronic inflammation and tissue damage. Unfortunately, allergic diseases belong to the group of the most common pathology of childhood and they are considered in modern society as a major medical and social problem [12]. The frequency of allergic diseases, according to different authors, varies widely, and atopic diseases such as asthma and atopic dermatitis are in the first place (they affect up to 20% of the population individually or in various combinations) in most industrialized countries.

Allergic diseases are chronically recurrent inflammatory diseases caused primarily by IgE-mediated allergic reactions and genetically associated with atopy [4]. However, the pathogenesis of allergic diseases is multifaceted and represents a rather complex system. In recent years, special attention has been paid to the study of non-inflammatory mechanisms underlying allergic diseases. It was found that metalloproteinases (MMP) play a significant role in the mechanisms of maintaining chronic inflammation and tissue remodeling [10]. For example, MMP-9 is involved in the processes of inflammation, repair and mobilization of matrix-related growth factors and cytokine processing. Substrates for MMP-9 include denatured type I collagen (gelatin), native collagens of types IV, V, VII, X and XI, fibrinogen, vitronectin, IL-1, and entactin which connects laminin and type IV collagen. Keratinocytes, monocytes, leukocytes, macrophages, and fibroblasts are sources of MMP-9. Basal levels of MMP-9 are usually low, it s expression can be induced by various cytokines/chemokines, including TNFα (tumor necrosis factor-alpha), and MMP-9 mainly secreted by inflammatory cells. The regulation of inflammation by gelatinases is carried out by cytokine/chemokine processing, since MMP-9 has a stimulating effect, and MMP-2 has an inhibitory effect on inflammation. The promoter region of MMP-9 has some functional binding sites of enhancers, such as NF-κB and AP-1 sites. These sites make MMP-9 capable of inducing Pro-inflammatory cytokines, especially TNFα, which is a key mediator in the pathogenesis and maintenance of chronic inflammation [1]. This gelatinase triggers a cascade of reactions of degradation of the extracellular matrix having the ability to destroy denatured collagen.

MMP-9 acts synergistically with other metalloproteinases in this case. This type of MMP can interact with various matrix proteins through its fibronectin-

like fragment being in the pericellular space. MMP-9 contributes to the creation of feedback between the state of the matrix and potential activation of MMP [1]. Therefore, the study of changes in the concentration of this enzyme in children with allergopathology represents the large practical and scientific interest.

Objective: to study the role of MMP-9 in the pathogenesis of allergic diseases in children.

Materials and methods

180 children aged from 1 to 18 years were examined. This study included patients suffering from bronchial asthma (n = 54), atopic dermatitis (n = 54) and combination of these pathologies (n = 72). The average age of the examined patients was 11.44±4.67 years. The control group consisted of 56 children of the I and IIa health groups comparable in gender and age, without clinical manifestations of allergic diseases and positive allergy history.

The diagnosis of bronchial asthma (BA) was made on the basis of the National program "Bronchial asthma in children. Strategy of treatment and prevention" (2017) [13]. The diagnosis of atopic dermatitis (AD) was verified on the basis of the clinical recommendations "Atopic dermatitis in children" (2016) [4].

The criteria for inclusion in this study were: the presence of a confirmed diagnosis of BA, AD or a combination of these diseases, the absence of concomitant chronic pathology from other organs and systems, (age under 18 years), Russian nationality, the presence of signed patient (aged over 15 years) or parents (for children under 15 years) informed consent to conduct the study.

Exclusion criteria: the presence of previously established chronic and acute diseases of the bronchopulmonary system (tuberculosis, acute tracheobronchitis, pneumonia, etc.) or skin, the age of patients older than 18 years.

All children passed a comprehensive clinical and laboratory examination on the basis of the pediatric Department of the clinic of the Rostov State Medical University. Serum levels of MMP-9 were determined by enzyme immunoassay using Cloud-CloneCorp® test systems (USA). The results of clinical, instrumental and laboratory studies of patients were correlated with the data of the ELISA study of the level of MMP-9 in blood serum.

The study was conducted in compliance with all ethical standards set out in WAME (the World Association of Medical Editors) and approved by the Local Ethics Committee of Rostov State Medical University.

Statistical processing of results was performed by using Microsoft Office Excel 2003 and Statistica 12.0 for Windows software package.

Results and discussion

Our study found that the values of MMP-9 in the examined patients with allergopathology in blood serum significantly exceeded the parameters set in the control group (Table 1).

The analysis of the obtained data showed that among patients with the established diagnosis of BA, the maximum concentration of this cytokine was registered in children with a moderate course of the disease 714.93 pg/mL (517.37-902.51), while with mild it was 569.0 pg/mL (377.79-825.29), and with severe – 2.89 pg/mL (121.35-362.91) (Figure 1).

The conducted correlation analysis showed the presence of a significant correlation between the severity of asthma and the level of control over the disease (r = 0.63). An inverse correlation was established between the concentration of MMP-9 and the severity of BA (r = -0.53).

Similar data was obtained in patients with a combination of BA and AD. Thus, in children of this group, there was also a significant increase in serum MMP-9 (596.285±82.169 pg/mL) compared with healthy patients (307.391±42.394 pg/mL) (p = 0.015). At the same time, the maximum indica-

TABLE 1. MMP-9 INDICATORS IN THE BLOOD SERUM OF THE EXAMINED PATIENTS

Diagnosis	MMP-9 indicators in blood serum, ng/mL	p
BA	489.20±59.52 431.76 (306.15-612.93)	$p_{1,4}$ = 0.023 $p_{2,4}$ = 0.042 $p_{3,4}$ = 0.019
AD	573.75±113.71 445.04 (266.43-790.06)	
BA + AD	596.29±82.17 473.02 (339.33-687.26)	
Control group	307.39±42.39 276.05 (160.33-397.02)	

Note. $p_{1,4}$, significance of differences between BA and control; $p_{2,4}$, significance of differences between AD and control; $p_{3,4}$, significance of differences between BA + AD and control.

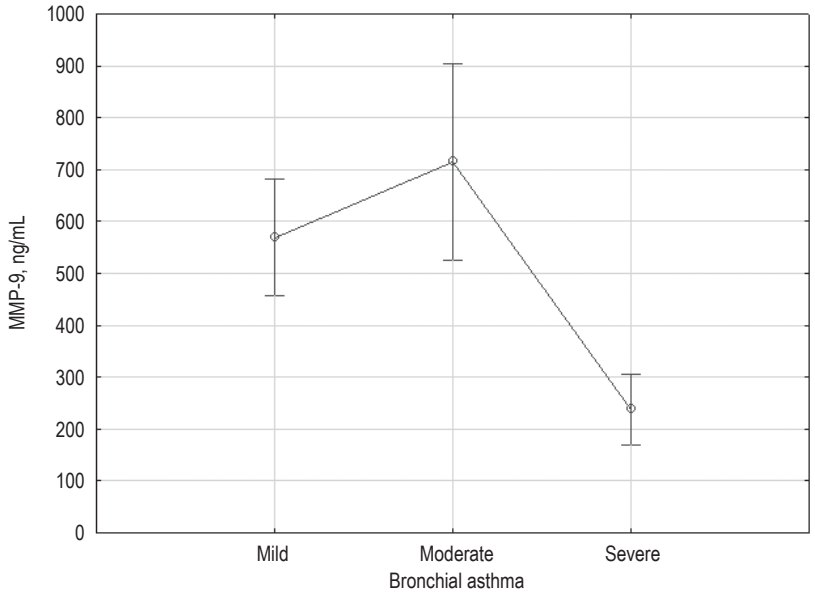

Figure 1. Concentration of MMP-9 in blood serum depending on the severity of BA

tors were registered in patients with moderate course of the disease (Table 2).

At the same time the MMP-9 values had no statistically significant differences between children with controlled (566.12 (424.94-687.26) pg/mL) and uncontrolled (376.55 (241.04-815.64) pg/mL) course of the disease ($p = 0.269$).

However, it is interesting to note that the concentration of this matrix metalloproteinase in serum was slightly higher (645.52±75.04 pg/mL) among children with polyvalent sensitization than in patients with monoallergic etiology of the disease (462.65±118.89 246.20 pg/mL) ($p = 0.272$).

The values of MMP-9 in patients with only skin manifestations of atopy were significantly higher (573.75±113.71 pg/mL) than in the control group (307.39±42.39 pg/mL) ($p = 0.025$). At the same time there were no differences depending on gender: the average values for girls were 538.09±119.64 or 385.24, while for boys – 680.73±324.17 pg/mL.

Analysis of indicators based on the severity of the disease showed that the patients in all three groups had a significant variation of MMP-9 indicators in blood serum. Meanwhile there were no significant differences in severity ($p \geq 0.05$).

However, there is a clear tendency to increase the concentration of MMP-9 in the blood serum of patients with changes in age-related forms of the disease. It was found that the maximum values of MMP-9 were registered among children with adolescent AD (1163.04±120.17 pg/mL), while with children the average values were 342.56±50.73, and with infants (924.71±124.74 pg/mL).

The results of our research are consistent with the data obtained by our foreign colleagues. Ko F.W. et al. conducted a study of the level of MMP-9 in patients with various degrees of BA severity and healthy patients. Scientists have found that uncontrolled moderate and severe asthma are associated with greater activity of proteolytic enzymes and, therefore,

TABLE 2. DISTRIBUTION OF MMP-9 INDICATORS IN THE BLOOD SERUM OF PATIENTS WITH AD AND BA DEPENDING ON THE SEVERITY OF AD, M±Err

Severity of BA	MMP-9 indicators, pg/mL	p
Mild BA	567.54±91.72 472.08 (424.32-598.46)	$p_{1,2} = 0.682$ $p_{1,3} = 0.042$ $p_{2,3} = 0.019$
Moderate BA	694.87±132.98 572.39 (413.77-776.06)	
Severe BA	222.47±18.81 235.87 (185.33-246.20)	

Note. $p_{1,2}$, significance of differences between mild and moderate BA; $p_{1,3}$, significance of differences between mild and severe BA; $p_{2,3}$, significance of differences between moderate and severe BA

despite a similar inflammation of the respiratory tract, this can play a significant role in the remodeling of the bronchi and accelerate the process of reducing lung function in these patients [10].

Maria P. Foschino Barbaro and her colleagues studied the concentration of MMP-9, pH, NO level in exhaled air, as well as inflammatory cells in sputum in patients suffering from BA. The results of the study showed a significant increase in the exhaled MMP-9 in patients compared to the control. It was noted that the maximum concentrations of MMP-9 were observed in patients with severe BA, compared with patients suffering from mild and moderate forms of the disease. An increase in MMP-9 was most frequently recorded in patients with neutrophilic inflammation of the respiratory tract. A correlation was also established between the exhaled MMP-9 and the percentage of neutrophils in sputum, FEV1, exhaled NO and PH. The obtained results indicate a significant role of MMP-9 in the pathogenesis of airway remodeling in asthma, and also suggest that monitoring MMP-9 in exhaled air can help not only to monitor the current airway remodeling, but also to recognize severe forms of BA in order to determine the appropriate choice of therapy in time [2]. This fact is confirmed by the research conducted by Grzela K. et al. [7, 9] it is important to note that an increase in the concentration of MMP-9 in exhaled air is accompanied by an increase in its concentration in the blood serum of patients with BA [3, 10].

A study conducted by the Bureau of Devillers A.C. and co-authors also found that MMP-9 plays an important role in maintaining allergic inflammation in AD. It has been shown that patients suffering from AD have a significant increase in the level of MMP-9 in the blood serum compared to the control group [5].

In the work of Harper J.I. and co-authors it was shown that MMP, and in particular MMP-9, represent an important potential component of AD pathology. Studies of washouts from AD-affected skin areas found that in samples obtained from patients, the activity of MMP is 10-24 times greater than in normal control skin ($p < 0.02$) and five times greater than in areas of unaffected AD skin taken from patients with this disease. A number of studies conducted by the author (gelatin cymography and analysis of the antibody array) revealed significant levels of MMP-9 in samples obtained in sick children, while lower levels of MMP-10 and tissue metalloproteinase inhibitors were observed, as well as low levels of MMP-1 (fibroblast collagenase), MMP-3 (stromelizin 1) and TIMP-4. The obtained research results once again prove the high significance of MMP in the pathogenesis of AD [8].

Conclusion

The data we obtained showed that all the patients we examined had a significantly increase in the level of MMP-9 in the blood serum, which indicates an important role of this cytokine in the pathogenesis of allergic diseases in children.

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