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## **THE ROLE OF HUMAN B-DEFENSIN 2 (HbD-2) AND CATHELICIDIN (LL-37) IN THE LOCAL PROTECTION OF THE UPPER RESPIRATORY TRACT IN CHILDREN WITH ALLERGIC RHINITIS AND BRONCHIAL ASTHMA**

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**Ключові слова:** *бронхіальна астма, алергічний риніт, антимікробні пептиди, діти, кателіцидин, людський дефензин бета-2, LL-37, HbD-2*

**Ключевые слова:** *бронхиальная астма, аллергический ринит, антимикробные пептиды, дети, кателицидин, человеческий дефензин бета-2, LL-37, HbD-2*

**Abstract.** *The role of human  $\beta$ -defensin 2 (HbD-2) and cathelicidin (LL-37) in the local protection of the upper respiratory tract in children with allergic rhinitis and bronchial asthma. Bolbot Yu.K., Bordii T.A., Vilenskyi Ya.V. Allergic diseases of the respiratory system seriously affect the psychological, physical and social aspects of live of sick children, morally and financially exhausting members of their families as well. It is known that exacerbations of allergic diseases of the respiratory tract occur due to interaction with numerous triggers, one of which is a respiratory viral infection. At the same time, it is widely known that patients with allergic respiratory diseases are more prone to acute respiratory infections. One of the reasons for this tendency often is an insufficient activity of non-specific factors of local immunity of the respiratory system – endogenous amphiphilic antimicrobial peptides, in particular the most studied their representatives - the family of defensins and human cathelicidin. Current research proves that these antimicrobial peptides are characterized by broad antiviral, antimicrobial and immunomodulatory activity. The aim of this study was to study the concentrations of local immune factors - human HbD-2 and LL-37 - in the secretion of the mucous membranes of the upper respiratory tract in children with asthma and allergic rhinitis and to clarify their role in protection against respiratory viral infections in this contingent of patients. We performed laboratory and clinical examinations of 76 children aged 7 to 18 years, of whom 24 were diagnosed with allergic rhinitis, 28 children - bronchial asthma, and 24 - bronchial asthma and allergic rhinitis. The control group consisted of 20 healthy children of the appropriate sex and age. In addition to general clinical methods, patterns of respiratory morbidity were analyzed and concentrations of antimicrobial peptides were determined: human cathelicidin (LL-37),  $\beta$ -defensin 2 (HbD-2) in the secretion of the upper respiratory tract by ELISA, statistical analysis was performed. It was found that children with allergic diseases of the respiratory tract are characterized by a higher frequency of acute respiratory infections with more frequent involvement of the lower respiratory tract, which led to an increase in the duration of the disease compared to their healthy peers. In children with allergic rhinitis and bronchial asthma, there was revealed a significant decrease in the concentrations of antimicrobial peptides in the secretion of the upper respiratory tract compared with the control group.*

**Реферат.** *Роль человеческого  $\beta$ -дефензина 2 (HbD-2) и кателицидина (LL-37) в местной защите верхних дыхательных путей у детей, больных аллергическим ринитом и бронхиальной астмой. Больбот Ю.К., Бордий Т.А., Виленский Я.В. Аллергические заболевания дыхательной системы серьезно влияют на психологические, физические и социальные аспекты жизни больных детей, а также морально и финансово истощают членов их семей. Известно, что обострение аллергических заболеваний респираторного тракта возникают из-за взаимодействия с многочисленными триггерами, одним из которых является респираторная вирусная*

инфекция. В то же время широко известно, что больные с аллергическими заболеваниями дыхательных путей более подвержены заболеванию ОРВИ. Одной из причин такой склонности сегодня все чаще называют недостаточную активность неспецифических факторов местного иммунитета респираторной системы – амфифильных эндогенных антимикробных пептидов, в частности наиболее изученных их представителей – семейства дефензины и человеческого кателицидина. Современные исследования доказывают, что данные антимикробные пептиды характеризуются широкой противовирусной, противомикробной и иммуномодулирующей активностью. Целью данного исследования стало изучение концентраций факторов местного иммунитета – человеческого HbD-2 и LL-37 – в секрете слизистых оболочек верхних дыхательных путей у пациентов, страдающих бронхиальной астмой и аллергическим ринитом и выяснения их роли в защите от респираторных вирусных инфекций у данного контингента больных. Мы провели лабораторное и клиническое обследование 76 детей в возрасте от 7 до 18 лет, из которых у 24 был диагностирован аллергический ринит, у 28 детей – бронхиальная астма, а у 24 – бронхиальная астма и аллергический ринит. Группой контроля были 20 здоровых детей соответствующего пола и возраста. Кроме общеобразовательных клинических методов, были проанализированы паттерны респираторной заболеваемости и определены концентрации антимикробных пептидов: человеческого кателицидина (LL-37),  $\beta$ -дефензины 2 (HbD-2) в секрете верхних дыхательных путей методом ИФА и проведен статистический анализ. Было установлено, что для детей с аллергическими заболеваниями дыхательного тракта характерна большая частота ОРВИ с более частым вовлечением нижних дыхательных путей, что приводит к увеличению продолжительности заболеваний по сравнению с их здоровыми сверстниками. У детей, больных аллергическим ринитом и бронхиальной астмой, выявлено существенное снижение концентраций обоих антимикробных пептидов в секрете верхних дыхательных путей при сравнении с контрольной группой.

Despite the significant advances in modern medicine, the problem of childhood bronchial asthma (BA) and allergic rhinitis (AR) continues to be a significant global medical and social burden in global pediatrics. Bronchial asthma continues to be one of the diseases that have the greatest impact on mortality rates and is associated with a high risk of disability. According to the WHO, among 15 million patients with disabilities, 1% are patients with asthma. According to various estimates, about a third of the adult European population suffers from AR, and its prevalence among children is estimated at about 40% [1, 9, 10]. In addition to a significant deterioration in the quality of life of patients, the presence of AR entails considerable financial costs. Data from the Asthma and Allergy Foundation of America confirm that in 2010 the cost of treating AR was approximately \$ 17.5 billion. Asthma and AR seriously affect the mental, physical and social aspects of the lives of sick children, can lead to serious complications, to disability, as well as morally and financially exhausting members of their families [6].

It is well known that exacerbations of allergic diseases of the respiratory tract occur due to interaction with numerous provoking factors. One of such factors is a respiratory viral infection, which can not only cause exacerbation of asthma and AR, but also significantly prolong and complicate their course. At the same time, it is known that patients with allergic respiratory diseases are more prone to SARS. One of the reasons for this tendency is the violation of the permeability of epithelial barriers due to the deficiency of their important components – nonspecific antimicrobial peptides (AMP). One of

the most studied endogenous cationic amphiphilic AMP is the family of human defensins and human cathelicidin (LL-37), which are secreted by keratinocytes, mucosal epitheliocytes, neutrophils, lymphocytes and monocytes [3, 8].

These AMP show a wide range of antimicrobial activity against both gram-negative and gram-positive bacteria, and also have antiviral activity. Thus, according to a number of studies, LL-37 is one of the key components of protection against respiratory syncytial (RS) virus, inducing direct damage to the viral envelope, disrupting the integrity of viral particles and thus reducing the binding of the virus to epithelial cells of a human being [7, 11], and defensins inhibit the penetration of influenza A viruses, herpes simplex viruses types 1 and 2 into the cell, destroy the viral envelope and inactivate the virions of the RS virus [7].

A number of authors believe that the decrease in the concentrations of endogenous AMP on the mucous membranes of the upper respiratory tract may be a factor contributing to the development of respiratory infections. At the same time, a significant increase in their levels in patients with active inflammatory process with a high probability may indicate their active participation in the inflammatory process [2, 4, 7].

In recent years, many publications have appeared in the medical scientific literature on the role of AMP in the development of infectious pathology of the respiratory tract in children, including recurrent. However, there are almost no studies on the state of AMP production by the mucous membranes of the respiratory tract in patients with allergic diseases.

Taking into account all the above, the aim of our work was to study the concentrations of local immune factors of human  $\beta$ -2 defensin (HbD-2) and cathelicidin (LL-37) in the secretion of the mucous membranes of the upper respiratory tract (URT) in children with asthma and allergic rhinitis, with various manifestations of the severity of allergic pathology.

#### MATERIALS AND METHODS OF RESEARCH

Our study was conducted on the basis of ME "Specialized Medical Rehabilitation Center for Children and Adolescents" DRC" from September 2018 to August 2019 (Director – Candidate of Medical Sciences TYu Kovalenko). The study was authorized by the Commission on Biomedical Ethics of the Dnipropetrovsk Medical Academy of the Health Ministry of Ukraine.

Laboratory and clinical examinations of 76 children aged 7 to 18 years were performed, of which 24 were diagnosed with allergic rhinitis, 28 – bronchial asthma, and 24 – bronchial asthma and allergic rhinitis. The control group included 20 clinically healthy children of the appropriate sex and age.

Inclusion criteria: written consent of parents to participate in the study, verified diagnosis of allergic rhinitis and/or bronchial asthma lasting at least 1 year, age – 7 to 18 years. Exclusion criteria: existing exacerbation of chronic allergic or non-allergic airway pathology, chronic, hereditary and congenital diseases of the bronchopulmonary system, probiotics taking, systemic or local antimicrobials for 1 month before the study, the presence of acute infectious disease at the time of the study.

The diagnosis of bronchial asthma and allergic rhinitis was established on the basis of the Unified Protocol of primary, secondary (specialized) medical care "Bronchial asthma in children" of the Ministry of Health of Ukraine No. 868 of October 8, 2013 and the Order of the Ministry of Health of Ukraine "On approval of protocols for diagnosis and treatment of allergies in children" No. 767 dated 27.12.2005.

Assessment of the anamnesis data was carried out by questioning the parents and studying the child's medical documentation. All children underwent standard clinical and laboratory examinations as required by relevant regulations, including determination of total immunoglobulin E (IgE) levels and analysis of causative allergens. Also during the last three years the nature of acute respiratory infections, their duration and frequency were analyzed and studied.

The levels of antimicrobial peptides in the secretion from URT were determined by enzyme-

linked immunosorbent assay (Hycult biotech, the Netherlands). Immunological tests were performed at the Medical and Diagnostic Center of LLC "Pharmacies of the Medical Academy", Dnipro (head of the laboratory – Candidate of Biological Sciences OV Bratus).

Statistical data processing was performed using standard packages of applied statistical analysis for Statistica for Windows v. 6.1 and Microsoft Excel. The normality of the distribution of quantitative indicators was checked using the Shapiro-Wilk criterion. Since the vast majority of the obtained data were characterized by a type of distribution that differs from normal, non-parametric indicators were calculated in the statistical analysis of the study results: quantitative data are presented as median (Me) and interquartile range (IQR) – Q1 (25th percentile) and Q3 (75<sup>th</sup> percentile). The Mann-Whitney test (U) was used to quantify the differences between independent groups for quantitative traits. The Kraskel-Wallis test was used to compare the three independent groups on one basis. To determine the relationship between the studied parameters, Spearman's rank correlation indices were calculated [5].

#### RESULTS AND DISCUSSION

Among the children included in the study, the vast majority were of primary and secondary school age (from 7 to 14 years), they accounted for 94%. The median age of the examined children was 11 (9; 12) years. We did not find a significant difference in age between children with different nosologies. Thus, in the group of children with AR the median age was 10.5 (10; 11) years, in the group of children with asthma – 9 (8; 12) years, and in the group of children with a combination of these nosologies – 11 (11; 12) years. After analyzing the gender composition of the respondents, we found that boys predominated in all age groups. But the most pronounced dominance was in the group of patients with asthma and AR. Thus, in the group with AR there were 41% of boys, in the group with asthma – 57%, and in the group with both nosologies – 83%.

Among patients with AR, the median duration of the disease was 5 (4; 6) years, and in the group with a combination of AR and asthma, it was 6 (5; 7) years. In isolated AR, patients with seasonal manifestations of the disease made up 58%, and in combination with asthma their proportion decreased to 42%. Moderate severity of rhinitis in isolated AR was registered in 54% of cases, in combination with asthma – in 53% of patients. Among patients with isolated AR, at the time of inclusion in the study,

75% received therapy. In the group of children with asthma and AR, 70.83% of patients received drug therapy for allergic rhinitis. Among the patients receiving therapy, in the group of children with AR the controlled course of rhinitis was observed in 94% of cases, and in the group of children with asthma – in 88% of cases. The controlled course of rhinitis in patients who did not receive therapy was observed in 83% of cases in the group of children with isolated AR and in 85% of cases in the group of children with BA + AR.

In the asthma group, the median duration of the disease was 5.5 (5; 6) years, in the group with a combination of BA and AR, it was 6 (6; 7) years. At the time of diagnosis, among patients with isolated asthma, patients with intermittent course predominated (53%). Mild persistent asthma was found in 28% of patients, and moderate asthma in 17%. In the group with a combination of BA and AR, the proportion of children with intermittent asthma was 66%, the remaining patients were diagnosed with mild persistent asthma (33%). Among patients with isolated asthma at the time of inclusion in the study 17% received therapy. Among children with asthma and AR 12% of patients received basic asthma therapy. Among patients receiving basic therapy in the group of children with asthma, controlled asthma was observed in 80% of cases, and in the group of children with BA + AR – in 66% of cases. Among patients who did not receive basic therapy, in the group of children with isolated asthma controlled course was observed in 91% of cases, and in the group of children with asthma + AR – in 85% of cases.

Causal-significant allergens in isolated AR are: pollen group of allergens in 55% of cases, epidermal group allergens – in 38%, mold group – in 26%, household dust allergens – in 7% of cases. As causative allergens in the group of asthma there were identified the following: pollen group – 62% of cases, epidermal – 33%, mold group – 20%, household dust allergens – in 25% of cases. In the case of a combination of nosologies of AR and BA, the structure of allergens was as follows: pollen group – 29%, epidermal allergens – 33%, molds – 12%, household dust allergens – 37%.

In most patients, eosinophilia and elevated total IgE levels were observed, confirming the atopic nature of the disease. We did not find a significant difference in the mean levels of eosinophilia and the mean levels of serum IgE concentrations between the groups.

The analysis of patterns of respiratory incidence rate revealed that in general for the last three years

children with allergic respiratory diseases had acute respiratory tract infections (URTI) more often than their healthy peers from the control group. The highest average frequency of acute respiratory diseases was found in patients with BA – 8 (6; 8) episodes per year. They were sick not only almost 2 times more often than children in the control group 2 (1; 3) episodes per year;  $p=0.005$ , but also significantly more often than children with AR – 6 (3.5; 8) episodes per year;  $p=0.01$ . The incidence of URTI was almost as high in the group with a combination of AR and BA – 6 (5.5; 10) episodes per year. Against the background of URTI, worsening of symptoms of allergic diseases, which required correction of the treatment plan, was observed in 81% of children in BA group, in 83% – in the BA + AR group and in 53% of patients in the AR group. This was accompanied by a prolongation of the average duration of one episode of URTI. This indicator was the highest in the group of children with BA and AR – 18 (17.5; 19) days, which is almost 2.5 times more than in the control group – 7 (7; 8) days ( $p=0, 01$ ), whereas in isolated BA the average duration of one episode of URTI was 14 (13; 14) days, and in AR – 10.5 (10; 11.5) days.

The median levels of HbD-2 concentrations in oral secretions in children with allergic diseases were significantly lower compared with the control group (Table): 1.2 times in children from the group of AR, 1.7 times in children from BA group and almost 2 times – in children with a combination of these nosologies. The differences in the levels of HbD-2 concentrations in the secretion of the oral cavity in children between some groups were also statistically significant ( $p=0.04$  for comparison of groups AR and (BA + AR);  $p=0.05$  for comparison of BA and (BA + AR)). Patients with AR showed the highest level of HbD-2 among all groups, while patients with combined pathology of BA + AR showed the lowest concentrations of HbD-2.

We found a significant decrease in the median levels of concentrations of LL-37 in the secretion of the oral cavity in patients of all study groups compared with the control group: 2 times in children from AR, 2.9 times in children from asthma and 2, 4 times in children with a combination of these nosologies. Significant differences in the level of LL-37 concentrations were also found when comparing the group of AR and BA ( $p=0.02$ ), as well as between the groups of AR and (BA + AR) ( $p=0.04$ ). The lowest levels of LL-37 were found in the group of patients with asthma.

**Median concentrations of antimicrobial peptides HbD-2 (pg/ml) and LL-37 (ng/ml) in the secretion from URT of children of the studied groups**

Groups	HbD-2, pg/ml	LL-37, ng/ml
AP (n=24)	195 (190;197)*	0.43 (0.41; 0.46)#
BA (n=28)	146 (129;179)*	0.33 (0.28; 0.34)#
BA+AR (n=24)	126 (119;136)*	0.36 (0.33; 0.38)#
Control (n = 20)	251 (248; 253)	0.89 (0.83; 0.92)

Notes: \* – p=0.03 when compared with the control group; # – p=0.02 when compared with the control group.

The correlation analysis showed that the levels of the studied AMP inversely depended on the severity of allergic pathology. Thus, the relationship of medium strength between the concentration of LL-37 in the secretion of the upper respiratory tract and the severity of AR ( $r = -0.68$ ,  $p < 0.05$ ), the severity of asthma,  $r = -0.54$ ,  $p < 0.05$ ), as well as between the concentration in the secretion of the oral cavity HbD-2 and the severity of AR ( $r = -0.64$ ,  $p < 0.05$ ). A strong negative relationship was observed between the concentration of HbD-2 in the secretion from the upper respiratory tract and the severity of asthma ( $r = -0.86$ ,  $p < 0.05$ ). Basic therapy taking at the time of the study showed a significant positive relationship with the levels of concentrations of both AMP (LL-37 ( $r = 0.32$ ,  $p < 0.05$ ), HbD-2 ( $r = 0.73$ ,  $p < 0.05$ )). However, we did not find an association between AMP concentrations and disease duration, eosinophilia levels, and serum IgE concentrations.

A study of the relationship between AMP levels and patterns of acute respiratory incidence in children with AR and BA revealed a negative association of moderate strength between the incidence of URTI over the past three years and LL-37 levels in BA patients ( $r = -0.66$ ,  $p < 0.05$ ), as well as a negative weak relationship between the concentrations of LL-37 and HbD-2 in the secretion from the oral cavity and the average duration of one case of URTI in asthma ( $r = -0.32$ ,  $p < 0.05$  and  $r = -0.49$ ,  $p < 0.05$ , respectively).

Thus, this study showed that patients with allergic respiratory diseases are characterized by lower content of LL-37 and HbD-2 in the secretion of the mucous membranes of the oral cavity than their peers, herewith this indicator largely depends

on the degree of allergic inflammation activity. On the other hand, low concentrations of protective peptides in our study were associated with an increase in the incidence of URTI and a prolongation of their episodes. Thus, possible ways of therapeutic correction may be, on the one hand – strengthening anti-inflammatory therapy of allergic diseases to achieve control of symptoms, and on the other – the use of drugs that can increase the production of protective peptides by mucous membranes – such as probiotics.

#### CONCLUSIONS

1. Children with allergic rhinitis and bronchial asthma are characterized by significantly lower levels of concentrations of both antimicrobial peptides in the secretion of the upper respiratory tract compared with the control group.

2. Children with allergic diseases of the respiratory system suffer from URTI significantly more often than children from the control group, they are also characterized by an increase in the average duration of one case of URTI.

3. It was found that the level of AMP concentrations has a positive effect on the use of basic therapy drugs, and negatively - the severity of allergic diseases and lack of control of symptoms.

4. There is a connection between the levels of AMP concentrations in the secretion of URT and the increase in the frequency and prolongation of acute respiratory infections in children from the asthma group.

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

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