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LEVELS OF IL-4 AND γ -INTERFERON IN CHILDREN'S BLOOD SERUM AS PREDICTORS OF ASTHMA FORMATION

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Summary

Introduction. *The prevalence of asthma continues to increase every year. Asthma is the leading chronic disease. Inflammation, both acute and chronic, is closely related to the action of cytokines (pro- and anti-inflammatory). T-helper 2 lymphocytes release IL-4, which triggers the production of immunoglobulin E (IgE) antibodies, which set the stage for allergy and activate inflammatory cells. The regulators of this process are T helper-1 lymphocytes, which produce cytokines (IFN-gamma) that suppress Th-2 activity. Disturbances in the ratio of Th-1/Th-2 lymphocyte clones are a subject of debate in the early detection of asthma and the prediction of the development of this disease.*

The aim of the study was to evaluate the levels of IL-4 and γ -interferon in the blood serum of children with transient wheeze and asthma.

Material and methods. 121 children were included in the study. The patients were divided into groups: group 1 – children with transient wheezing (TW) ($n = 81$), group 2 – children with doctor-diagnosed asthma (DDA) ($n = 15$), group 3 – healthy children ($n = 25$).

IL-4 and γ -interferon in blood serum were analyzed by ELISA using commercial kits (human IL-4 and human γ -interferon "Vector Best-Ukraine"). Data were analyzed using Statsoft Statistica version 8 (Tulsa, OK) and the MedCalc version 17.2 statistical program.

The planned clinical trials were conducted after obtaining the approval of the local ethics committee (date: February 1, 2015; number: 2015/01) and were conducted in accordance with the principles of the Declaration of Helsinki, as amended in October 2013.

This article was conducted within the framework of the Department of Pediatrics No. 2 of Kharkiv National Medical University «Medical and biological aspects of adaptation of children with somatic pathology to modern conditions. Prediction of asthma control in children taking into account inflammatory markers and the state of the airway barrier of the lungs» (state registration number 0120U102471).

Results. *It was found that in children of the first and second groups, in the midst of clinical manifestations of wheezing, IL-4 levels significantly increased and serum γ -interferon levels decreased. The highest levels of IL-4 and the lowest levels of serum γ -interferon were found in patients with DDA.*

Serum levels of IL-4 above 15.33 pg/mL and γ -interferon below 98.62 pg/mL in children with wheezing episodes may be considered as a possible indicator of asthma development.

Conclusions. *Serum IL-4 and γ -interferon are involved in the regulation of allergic inflammatory processes in the body. A statistically significant increase in IL-4 levels and a decrease in γ -interferon levels in the blood serum of patients with asthma is likely to indicate the development of a chronic form of inflammation.*

Key words: Asthma; Transient wheezing; IL-4; γ -interferon; Children.

Introduction

The prevalence of asthma has increased in recent years. This nosologic form is one of the most common chronic diseases [1] and has many different phenotypes and triggers for its development and progression [2, 3]. The heterogeneity of asthma is manifested by different degrees of bronchial obstruction, a wide variety of clinical symptoms, different frequencies of exacerbations and individual responses to basic therapy [2-4]. First of all, asthma is an inflammatory process in the bronchial wall, which is a chronic inflammation of the bronchi that persists even in the asymptomatic period [5,6]. According to the type of inflammatory process, there are four main mechanisms, such as eosinophilic, neutrophilic, mixed granulocytic and pauci-granulocytic [7-9].

The onset of asthma usually occurs in childhood. According to current research, the onset of this disease begins before the age of three in almost 50% of patients [10,11].

The manifestations of asthma debut in children are repeated episodes of bronchial obstruction. Diagnosing

the onset of asthma in children under 6 years of age has a number of limitations related to the difficulty of identifying the wheeze phenotype at this age [12]. Repeated episodes of bronchial obstruction have a variety of etiologic factors and are manifestations of many nosologic forms [13]. They are observed in the presence of foreign bodies in the bronchopulmonary system, in diseases of the gastroesophageal zone, can be manifestations of congenital heart and great vessels, congenital diseases affecting metabolic processes, etc. To date, no reliable biomarkers have been identified to distinguish non-asthmatic wheezing from asthma, especially in young children. Various asthma prediction models are practical management tools for use in clinics for children under 5 years of age with recurrent wheezing, but their sensitivity and specificity are limited, especially in cases where wheezing episodes are infrequent [14].

The study of external respiratory function, which is one of the main studies to confirm the diagnosis, has certain difficulties in children of this age group [1].

New research raises new questions for the scientific community. The search for asthma biomarkers is a priority for scientists. Not only timely diagnosis and correct therapy, but also the quality of the patient's future life depends on their information content [15].

The discovery of a biological marker that could predict the development of asthma would be of great clinical importance. To date, researchers have used a sufficient number of biomarkers of asthma and chronic allergic inflammation, namely: fractional concentration of exhaled nitric oxide (FeNO) [16], blood eosinophils, sIgE, periostin, von Willebrand factor [17] and others, but none of them has been recognized as ideal [18, 19].

To date, there is no reliable biological marker for the diagnosis of asthma in preschool children.

Therefore, the expansion of diagnostic criteria for the early detection of asthma and prediction of its development remains relevant at the present stage.

It is known that the most common mechanism for the development of chronic inflammation in children is the development of eosinophilic asthma [20, 21]. The central cytokine responsible for allergic inflammation is IL-4 [22]. It is considered to be one of the most important anti-inflammatory cytokines that regulates B-cell differentiation, promotes IgE secretion, eosinophil accumulation in the peripheral blood, and directs the differentiation of T lymphocytes into type 2 helper T cells (Th2 helpers) [23, 24]. On the other hand, the immune response link in the differentiation of lymphocytes into type 1 T helper cells (Th1 helper cells) undergoes reverse changes. We can judge this indirectly by the level of γ -interferon. One of the functions of γ -interferon is to stimulate the immune response to fight viral infections. γ -Interferon is almost the only representative of type II interferons specific for type I activation of immune system cells [25]. Although B lymphocytes are responsible for the humoral response of the immune system, there are studies confirming the production of γ -interferon by B lymphocytes in response to bacterial infections, promoting macrophage activation [26]. Recent studies have provided conflicting information regarding γ -interferon levels in asthma [27, 28]. In our study, we performed a diagnostic and prognostic assessment of serum levels of IL-4 and γ -interferon in children with transient wheezing (TW)

and doctor-diagnosed asthma (DDA) and evaluated the relationship between these parameters.

Material and methods

Study design. This was a longitudinal cohort study from 2016 to 2020, including children with recurrent wheezing who were treated and evaluated in a pediatric clinic.

Inclusion criteria: informed consent signed by the patient's parents; patient's age from 1.5 to 6 years; current wheeze episode during the stay is the third or more.

Exclusion criteria: congenital and chronic cardiopulmonary or neurological diseases; hereditary diseases leading to changes in the functioning of the respiratory tract, including cystic fibrosis; proven immunodeficiency; confirmed or suspected acute or chronic bacterial respiratory tract infection; suspected or confirmed gastroesophageal diseases; previous treatment with anti-leukotriene drugs or systemic corticosteroids, patients who received intravenous therapy less than 48 hours before the study.

The first phase of the study included 100 patients between the ages of 1.5 and 6 years. Patients met the inclusion criteria and had no exclusion criteria. Patients received specific treatment according to the GINA 2019 global guidelines. All patients underwent clinical history, physical examination, and laboratory evaluation. Serum levels of IL-4 and γ -interferon were also tested. The control group consisted of 25 healthy children (of similar age and sex) with no signs of chronic diseases and no signs of acute illnesses in the previous three months, who had come to the hospital for routine check-ups or vaccinations. The parents of all patients and children in the control group were informed about the objectives of the study, and written informed consent was obtained from both parents before enrollment.

In the second phase of the study, patients were contacted repeatedly for examination when they reached the age of 6 years. 4 patients were lost to follow-up (one changed his telephone number, two moved to another country, and the parents of one child refused to continue participation in the study) Thus, 96 children (96%) were included in the second phase of the study. (Fig. 1).

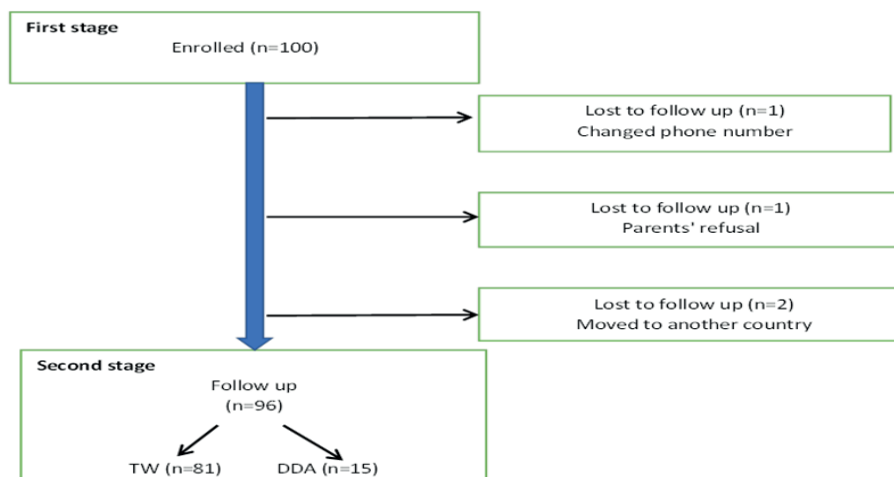


Fig. 1. Flow diagram illustrating the study design and procedures of the IL-4 and γ -interferon levels in the blood serum of children. TW – transient wheezing, DDA – doctor-diagnosed asthma.

The inclusion and exclusion criteria were reviewed. Informed consent was re-signed for continued participation in the study. After re-evaluation of the criteria, 96 patients were included in the study. Medical history was reassessed based on the GINA 2019 guidelines and included symptoms (cough and wheeze) for more than 10 days during an upper respiratory tract infection, more than 3 episodes of wheeze per year, coughing between episodes, and the presence of atopic dermatitis or food allergies or a family history of asthma. Patients diagnosed with asthma during this period and children diagnosed with asthma at a follow-up visit were identified.

The diagnosis of asthma was made by a pediatric respiratory specialist (pulmonologist or allergist) according to GINA guidelines. In children younger than 5 years, the diagnosis of asthma was based on recurrent wheeze, history of allergic disease, allergen sensitization, history of asthma in first-degree relatives, response to bronchodilators, and clinical improvement within 3 months of ICS use; in children older than 5 years, the diagnosis of asthma was based on typical respiratory symptoms and pulmonary function test results.

After the diagnosis was confirmed, the children were divided into 2 groups. The first group included 81 patients with transient wheeze (TW), whose wheeze symptom stopped during the follow-up, and the second group included 15 children with doctor-diagnosed asthma (DDA).

Investigation of blood serum levels of IL-4 and γ -interferon. The levels of IL-4 and γ -interferon in the blood serum of patients and controls were determined at the first stage of clinical work.

Serum levels of IL-4 and gamma interferon in patients were determined during the first 2 days of clinical manifestations of bronchial obstruction, before the start of therapy. Blood samples were taken in the morning, before meals, using standard venipuncture technique or from a venous catheter, if available. Blood samples were collected by a trained pediatric phlebotomist nurse. Blood was collected in special tubes containing a coagulation activator and gel. After collection, samples were centrifuged at 1300 rpm for 10 minutes. Frozen samples were stored at $-300C$ until the study. 6 months after the initial sample collection, the serum in the tubes was simultaneously thawed and tested for IL-4 and γ -interferon.

IL-4 in serum was analyzed by ELISA using commercially available kits (Human IL-4, Vector Best-Ukraine, catalog number: A-8754), and γ -interferon in serum was analyzed by ELISA using commercially available kits (Human γ -interferon, Vector Best-Ukraine, catalog number: A-8752).

Statistical analysis. All statistical analyses were performed using StatSoft STATISTICA version 8 (Tulsa, Oklahoma) and MedCalc version 17.2 statistical software. The Shapiro-Wilk test was used, and the histogram and q-q plot were examined to assess normality. The median (Me) and interquartile range (Lq - lower quartile; Uq - upper quartile) were determined, taking into account that the sample distribution differed from normal. The non-parametric Mann-Whitney U test (MW) was used to compare two samples, and χ^2 , Fisher's exact test, was

used to calculate two relative indices. The difference in parameters compared at two points was considered statistically significant at $p < 0.05$. When comparing indicators characterized by a comparison of more than 2 points, the H criterion of Kruskal-Wallis (KW) analysis of variance was used, and differences were considered significant with the Bonferroni correction. Correlations between parameters were determined using Spearman's rank correlation analysis (r); $p < 0.05$ was considered a statistically significant difference. Receiver operating characteristic (ROC) curves were plotted for the variables to determine optimal cutoff values for endpoint prediction. Statistical «thresholds» were calculated by minimizing the distance between the point with specificity=1 and sensitivity=1 and the various points on the ROC curve. For ROC analysis, an area under the curve (AUC) of 1.0 indicates perfect discrimination, while an area of 0.5 indicates that the test discriminates no better than chance. The cut-off point of each variable and the sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of that cut-off point were determined using the AUC. To determine the most reliable screening tool among these four variables, a pairwise comparison of these variables was performed by determining the differences in area under the curve using the Hanley and McNeil method.

The planned clinical trials have been approved by the local ethics committee (date: February 1, 2015; number: 2015/01) and will be conducted in accordance with the tenets of the Declaration of Helsinki as amended in October 2013.

Results of study

Of the 96 patients with recurrent wheezing studied, 84.38% were children with TW who were free of wheezing symptoms at follow-up and 15.62% were children with DDA. When the groups were compared by age and sex, no significant difference was found in the need for oxygen therapy during wheezing. The relative number of patients with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at the peak of clinical symptoms did not differ between groups. History of atopic dermatitis and food allergy in childhood, allergic diseases and asthma in relatives, and onset of wheezing in the first year of life were significantly more frequent in patients with DDA. Elevated eosinophil counts and high Ig E levels in laboratory data were more frequent in patients with asthma (Table 1).

Serum levels of IL-4 and γ -interferon. Statistical processing using the Kruskal-Wallis test revealed that the H-criterion for such parameters as IL-4 levels ($H=55.4226$; $p < 0.001$) and γ -interferon ($H=69.9710$; $p < 0.001$) was significantly high, i.e. the statistical characteristics of the relevant indicators of different groups differ significantly, and the levels of these indicators depend on the patient's belonging to one group or another. It was found that serum IL-4 levels were elevated in children of both groups compared with the control group, and the highest levels were observed in children with DDA. At the same time, γ -interferon levels decreased in children of both groups, and the lowest levels were observed in patients with DDA (Table 2).

Table 1

The main group clinical and laboratory data

| Sign | TW | DDA | p |
|--|-------------------|-------------------|----------|
| Sex, M/F | 48/33 | 10/5 | p>0.05 |
| Age, years at recruitment Me (Lq; Uq) | 2.58 (1.55; 4.10) | 2.00 (1.50; 3.11) | p>0.05 |
| Age, years at follow-up Me (Lq; Uq) | 7.09 (6.00; 9.90) | 6.50 (6.00; 7.80) | p>0.05 |
| Presence of atopic dermatitis and food allergy in children | 45.7% (37/81) | 86.7% (13/15) | p=0.0018 |
| Positive family allergic history and asthma in relatives | 6.2% (5/81) | 73.3% (11/15) | p<0.001 |
| Onset of wheezing of the first year of life | 48.1% (39/81) | 80.0% (12/15) | p=0.0267 |
| Oxygen therapy during wheezing | 9.9% (8/81) | 13.3% (2/15) | p=0.3641 |
| High eosinophil blood parameters, cells, μ l | 8.7% (7/81) | 60.0% (9/15) | p<0.001 |
| Ig E increase, IU/ml (more than 50 IU/ml) | 25.9% (21/81) | 86.7% (13/15) | p<0.001 |
| ESR increase, mm/hour (more than 15 mm/hour) | 32.1% (26/81) | 33.3% (5/15) | p=0.4697 |
| CRP, mg/l (more than 6 mg/l) | 19.7% (16/81) | 13.3% (2/15) | p=0.2632 |

Table 2

Levels of IL-4 and γ -interferon in the blood serum of children with recurrent wheezing during the peak of clinical manifestations, Me (Lq; Uq)

| Parameter | Children(n=121) | | | Probability of difference and significance level |
|-----------------------------|----------------------------|-------------------------|----------------------------|---|
| | TW (n=81) | DDA (n=15) | Control (n=25) | |
| IL-4, pg/ml | 7.56 (4.35; 10.02) | 32.14 (19.34; 36.19) | 3.71 (3.10; 4.00) | $p_{TW-A} = 0.0001$ $p_{TW-control} = 0.0010$ $p_{A-control} < 0.001$ |
| γ -interferon, pg/ml | 113.97 (106.48; 120.09) | 81.42 (78.26; 89.63) | 130.24 (120.79; 130.81) | $p_{TW-A} < 0.001$ $p_{TW-control} = 0.0023$ $p_{A-control} < 0.001$ |

Correlation between IL-4 and γ -interferon parameters. The correlation between IL-4 and γ -interferon levels in all children with recurrent wheezing (n=96) was $r=-0.68$, $p<0.001$. The correlation between the parameters in children with asthma (n=15) was statistically significant – $r=-0.58$, $p<0.001$. Calculation of the correlation in children with transient wheezing (n=81) did not show a statistical relationship – $r=-0.01$, $p>0.005$.

Statistical processing was performed to determine the prognostic significance of serum levels of IL-4 and γ -interferon. The relationship between the levels of the indicators in early episodes of wheezing and the development of asthma was revealed. The «cut-off» points of these levels were determined with reliable indicators of sensitivity and specificity of the method (Table 3).

Table 3

Prognostic criteria for IL-4 and γ -interferon

| Parameter | AUC | «cut-off» point | Se, % | 95% CI | Sp, % | 95% CI | +LR | -LR |
|-----------------------------|-------|-----------------|--------|------------|-------|-----------|------|-------|
| IL-4, pg/ml | 0.932 | > 15.33 | 93.33 | 68.1-99,8 | 78.79 | 61.1-91,0 | 4.40 | 0.085 |
| γ -interferon, pg/ml | 0.954 | \leq 98.62 | 100.00 | 78.2-100.0 | 77.78 | 60.8-89.9 | 4.50 | 0.00 |

Discussion. In the present study, serum IL-4 levels were elevated in all patients with recurrent wheeze, with the highest levels in children who had developed asthma. This was considered a manifestation of allergic inflammation, since IL-4 stimulates an increase in IgE production and promotes the accumulation of eosinophils in the peripheral blood and tissues [23, 24]. This is supported by existing studies demonstrating the presence of allergic inflammation in patients with atopic dermatitis [29] and allergic rhinitis [30] in children and asthma in adults [31]. Our study included preschool children with a history of recurrent

wheezing who were diagnosed with physician-diagnosed asthma or transient wheezing by 6 years of age. Serum IL-4 levels were elevated in patients with transient wheezing compared to the control group and significantly elevated in children with asthma. Therefore, based on scientific studies, it can be assumed that increased levels of IL-4 in the blood serum of such patients not only indicate the allergic nature of the inflammation, but are also a manifestation of chronic allergic inflammation, in our case – bronchi.

We found that γ -interferon levels were reduced in children with recurrent wheezing. The lowest levels were

found in children with asthma. γ -Interferon is known to be produced by class 1 T helper cells. It is also one of a number of proteins that lead to a variety of cellular reactions that stimulate antiviral activity, and is the only representative of type II interferons with specific, pronounced antiviral activity [25,32]. In addition, γ -interferon has the ability to inhibit the secretory activity of class 2 T-helper cells. Given this, a decrease in serum γ -interferon levels is likely to be associated with an increase in class 2 T helper cell activity, which can be indirectly considered as a manifestation of allergic inflammation. There are scientific studies that show a decrease in γ -interferon levels in children who are frequently ill [33]. A decrease in γ -interferon levels has been shown to correspond to an eosinophilic type of inflammation in adult mice with asthma [34]. We found reduced levels of γ -interferon in patients with wheezing not associated with viral triggers. We interpreted the decrease in γ -interferon levels in children under 6 years of age with recurrent wheezing as a possible manifestation of chronic allergic inflammation.

We found an inverse relationship between the levels of IL-4 and γ -interferon, which is logical given the relevance of these indicators for different types of immune response. At the same time, statistically significant relationships were found in patients with physician-diagnosed asthma. Similar relationships have been demonstrated in recent scientific studies of chronic inflammation in asthma in mice [27, 34]. The present study confirms a significant feedback in children with chronic allergic inflammation.

The ROC analysis allowed us to determine the cutoff values of IL-4 and gamma-interferon in blood serum that had prognostic significance for the development of asthma. It was found that the criterion of IL-4 >15.33 pg/mL and γ -interferon \leq 98.62 pg/mL had prognostic significance for the development of asthma in children with recurrent wheezing.

This study has several limitations. First, about 46% of the children had comorbidities such as atopic dermatitis or food allergy, which may have influenced the increase in serum IL-4 levels. Thus, the levels of this cytokine that we obtained in children with asthma may have been higher due to concomitant allergic diseases [22]. Another limitation of the study is that asthma is a heterogeneous disease with many phenotypes. There are types that have a neutrophilic and paucibranch phenotype in the mechanism of development. The most common is the eosinophilic type of inflammation, which is associated with eosinophilic cell infiltration and thickening of the basement

membrane zone. The study conducted and the cytokines selected reflect this type of inflammation. That is, this study took into account the eosinophilic phenotype.

Conclusions

1. Serum IL-4 levels were significantly increased in children at the peak of wheezing. The highest serum IL-4 levels were found in children with asthma.

2. The level of γ -interferon in blood serum was statistically significantly reduced in children with recurrent wheezing. The lowest levels were found in children with asthma. Low levels of γ -interferon indirectly indicate the presence of allergic inflammation.

3. IL-4 and γ -interferon, as well as their interaction in asthma, are involved in the regulation of allergic inflammatory processes in the body and have an impact on the formation of chronic airway inflammation.

4. Levels of IL-4 higher than 15.33 pg/mL and γ -interferon lower than 98.62 pg/mL in the blood serum of children with wheezing episodes can be considered as a possible indicator for predicting the development of asthma.

Prospects for further research: determination of criteria for early diagnosis of asthma in children with recurrent wheezing.

Connection of the publication with planned research works

This article was written within the framework of the Department of Pediatrics No. 2 of Kharkiv National Medical University «Medical and Biological Aspects of Adaptation of Children with Somatic Pathology to Modern Conditions. Prediction of asthma control in children taking into account inflammatory markers and the state of the airway barrier of the lungs» (state registration number 0120U102471).

Conflict of interest. All listed authors have contributed sufficiently to the project to be included as authors, and all those qualified to be authors are listed in the author byline. To the best of our knowledge, there are no conflicts of interest, financial or otherwise. We have included acknowledgements, conflicts of interest, and funding sources after the discussion.

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РІВНІ ІЛ-4 ТА Г-ІНТЕРФЕРОНУ В СИРОВАТЦІ КРОВІ ДІТЕЙ ЯК ПРЕДИКТОРИ ФОРМУВАННЯ БРОНХІАЛЬНОЇ АСТМИ

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Резюме

Розповсюдженість астми продовжує зростати із року в рік. Серед хронічних захворювань астма займає лідируючу позицію. Формування запалення, як гострого так і хронічного, тісно пов'язане з дією цитокінів (прозапальних та протизапальних). Т-хелпери-2 -лімфоцитів вивільнює ІЛ 4, що запускає вироблення імуноглобуліну-Е (IgE) антитіл, які створюють умови для виникнення алергії та активують запальні клітини. Регуляторами цього процесу є Т-хелпери-1 лімфоцитів, які генерують цитокіни (IFN-gamma), що пригнічує активність Th-2. Порушення співвідношення клонів Th-1/Th-2-го типу лімфоцитів є предметом для дискусій, щодо раннього виявлення астми та прогнозування формування цього захворювання.

Метою дослідження було оцінити рівні ІЛ-4 та γ -інтерферону в сироватці крові дітей з transient wheezing та хворих на астму.

Матеріал та методи дослідження. У дослідженні взяли участь 121 дитина. Пацієнтів розподілили на групи: 1 група – діти з transient wheezing (TW) (n = 81), 2 група – діти з лікар-діагностованою астмою (DDA) (n = 15), 3 група – практично здорові діти (n = 25).

ІЛ-4 та γ -інтерферон в сироватці крові були проаналізовані методом ELISA за допомогою комерційних наборів (Human ІЛ-4 та Human γ -інтерферон «Вектор Бест-Україна»).

Проведено аналіз даних за допомогою Statsoft Statistica версії 8 (Tulsa, OK) та статистичної програми MedCalc версії 17.2.

Заплановані клінічні дослідження були проведені після отримання схвалення місцевого комітету з етики (протокол № 2015/01 від 1.02.2015 р.) і проводилися відповідно до принципів Гельсінської декларації, зміненої в жовтні 2013 року.

Дане дослідження виконано в рамках НДР кафедри педіатрії № 2 Харківського національного медичного університету «Медико-біологічні аспекти адаптації дітей з соматичною патологією в сучасних умовах. Прогнозування контролю бронхіальної астми у дітей з урахуванням маркерів запалення та стану аерогематичного бар'єру легень» (номер державної реєстрації 0120U102471).

Результати дослідження. Було встановлено, що у дітей першої та другої груп у розпалі клінічних проявів wheezing вірогідно підвищувалися рівні ІЛ-4 та знижувалися рівні γ -інтерферону у сироватці крові. Найвищі показники ІЛ-4 та найнижчі показники γ -інтерферону сироватки крові були виявлені у пацієнтів з DDA.

Рівні ІЛ-4 вище ніж 15,33 пг/мл та γ -інтерферону нижче ніж 98,62 пг/мл в сироватці крові у дітей з рецидивами wheezing можна розглядати, як можливий показник формування астми.

Висновки. ІЛ-4 та γ -інтерферон у сироватці крові приймає участь у регулюванні алергійних запальних процесів в організмі. Статистично значуще підвищення рівня ІЛ-4 та зниження рівня γ -інтерферону у сироватці крові пацієнтів з астмою імовірно вказує на формування хронічної форми запалення.

Ключові слова: бронхіальна астма; транзиторий візінг; ІЛ-4; γ -інтерферон; діти.

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