

The relationship of serum IL-18 levels with body mass index, the presence of obstructive disorders in children and adolescents with bronchial asthma

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Abstract

Introduction. Bronchial asthma (BA) in combination with obesity is a complex phenotype, an important pathogenetic factor in the formation of which is low-intensity systemic inflammation accompanied by the secretion of a spectrum of proinflammatory cytokines, including interleukin-18 (IL-18). However, the effect of IL-18 on the formation of bronchial obstruction syndrome in children and adolescents with BA obesity cannot be considered established.

Objective: to study the content of IL-18 in blood serum in children and adolescents with asthma and its relationship with the body mass index of patients, taking into account obstructive disorders.

Materials and methods. A single-center observational cross-sectional pilot study was conducted. 85 patients with asthma aged from 8 to 17 years were examined. Anthropometric and spirometric parameters were measured, and serum IL-18 levels were assessed. The study participants were divided into 2 groups: 1 — patients with low and normal body weight, 2 — overweight and obese.

Results. A direct statistically significant correlation was established between the level of IL-18 in blood serum and zBMI, $R = 0.30$, $p = 0.008$. In the general group and in patients with obstructive disorders, the level of IL-18 was statistically significantly higher in group 2 compared with group 1, 247.0 [207.0; 334.5] against 208.0 [134.0; 293.0] pg/ml, $p = 0.012$ and 349.0 [176.0; 452.0] versus 212.0 [148.0; 250.0] pg/ml, $p = 0.02$, respectively. In the absence of obstructive disorders, the level of IL-18 was comparable in children of these groups, 242.0 [194.5; 313.0] and 204.0 [134.0; 304.0] pg/ml, $p = 0.282$.

In patients of the second group and in the general group, the level of IL-18 was statistically significantly higher in the presence of obstructive disorders, 227.5 [171.0; 352.5] versus 223.0 [163.0; 307.0] pg/ml, $p = 0.048$ and 349.0 [176.0; 452.0] versus 242.0 [194.5; 313.0] pg/ml, $p = 0.046$.

Conclusion. In patients with asthma and overweight or obesity, the presence of bronchial obstruction is characterized by a statistically significantly higher level of IL-18 in blood serum compared with patients without bronchial patency disorders. This may indicate the inclusion of this interleukin in the genesis of bronchial obstruction in overweight and obese patients.

Keywords: bronchial asthma, obesity, spirometry, interleukin-18, children

Conflict of interests:

The author declare no conflict of interest.

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Взаимосвязь уровня сывороточного ИЛ-18 с индексом массы тела, наличием обструктивных нарушений у детей и подростков с бронхиальной астмой

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Аннотация

Актуальность. Бронхиальная астма (БА) в сочетании с ожирением представляет собой сложный фенотип, важным патогенетическим фактором формирования которого является низкоинтенсивное системное воспаление, сопровождающееся секрецией спектра провоспалительных цитокинов, включая интерлейкин-18 (ИЛ-18). Однако влияние ИЛ-18 на формирование синдрома бронхиальной обструкции у детей и подростков с БА и ожирением нельзя считать установленным.

Цель исследования: изучить содержание ИЛ-18 в сыворотке крови у детей и подростков с БА и его взаимосвязь с индексом массы тела пациентов с учетом обструктивных нарушений.

Материалы и методы. Было проведено одноцентровое наблюдательное поперечное пилотное исследование. Обследовано 85 пациентов с БА в возрасте от 8 до 17 лет. Проведено измерение антропометрических и спирометрических показателей, оценка уровня сывороточного ИЛ-18. Участники исследования разделены на 2 группы: 1-я — пациенты с пониженной и нормальной массой тела, 2-я — с избыточной массой тела и ожирением.

Результаты. Установлена прямая статистически значимая корреляционная взаимосвязь между уровнем ИЛ-18 в сыворотке крови и zИМТ, $R = 0,30$, $p = 0,008$. В общей группе и у пациентов с наличием обструктивных нарушений уровень ИЛ-18 был статистически значимо выше в группе 2 по сравнению с группой 1, 247,0 [207,0; 334,5] против 208,0 [134,0; 293,0] пг/мл, $p = 0,012$ и 349,0 [176,0; 452,0] против 212,0 [148,0; 250,0] пг/мл, $p = 0,02$, соответственно. При отсутствии обструктивных нарушений уровень ИЛ-18 был сопоставим у детей данных групп, 242,0 [194,5; 313,0] и 204,0 [134,0; 304,0] пг/мл, $p = 0,282$.

У пациентов второй группы и в общей группе уровень ИЛ-18 был статистически значимо выше при наличии обструктивных нарушений, 227,5 [171,0; 352,5] против 223,0 [163,0; 307,0] пг/мл, $p = 0,048$ и 349,0 [176,0; 452,0] против 242,0 [194,5; 313,0] пг/мл, $p = 0,046$.

Выводы. У пациентов с БА и избыточной массой тела или ожирением наличие бронхиальной обструкции характеризуется статистически значимо более высоким уровнем ИЛ-18 в сыворотке крови по сравнению с пациентами, не имеющими нарушений бронхиальной проходимости. Это может свидетельствовать о включении данного интерлейкина в генез бронхиальной обструкции у пациентов с избыточной массой тела и ожирением.

Ключевые слова: бронхиальная астма, ожирение, спирометрия, интерлейкин-18, дети

Конфликт интересов:

Автор заявляет об отсутствии конфликта интересов.

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INTRODUCTION

Bronchial asthma (BA) combined with obesity is a complex phenotype, an important pathogenetic factor in the formation of which is low-intensity systemic inflammation induced by excess adipose tissue, accompanied by the secretion of a spectrum of proinflammatory cytokines, including interleukin-18 (IL-18) [1, 2]. This disease phenotype is characterized by reduced disease control and insufficient efficacy

of therapy aimed at relieving T2-dependent inflammation [1]. It is assumed that the cause of the torpid course of BA associated with obesity is low-intensity systemic inflammation generated by excess adipose tissue [3]. Adipocytes and macrophages in adipose tissue secrete various proinflammatory cytokines, including interleukin-18 (IL-18), which may potentially affect the pathogenesis of the “asthma and obesity” phenotype [4].

The role of IL-18 in the pathogenesis of the BA phenotype combined with obesity is currently under debate. Studies by Zhang H. et al., Wong C. K. et al., and Tanaka H. et al. have demonstrated a relationship between the course of BA and serum IL-18 levels in adult patients [5–7]. Studies by C. Jung et al. have shown an increase in IL-18 levels in obese children [8]. It has also been found that IL-18 levels rise in people with metabolic syndrome [9]. However, studies of IL-18 levels in patients with combined asthma and obesity are few and far between and only concern adult patients [10]. Thus, at present, the influence of IL-18 on the development of bronchial obstruction syndrome in children and adolescents with the “asthma and obesity” phenotype cannot be considered established.

STUDY OBJECTIVE: to study the content of IL-18 in the blood serum of children and adolescents with bronchial asthma and its relationship with the patients' body mass index and the presence of obstructive disorders.

MATERIALS AND METHODS

Study design

A single-center observational cross-sectional study was conducted.

Terms and conditions of the study

The study was conducted at Children's City Clinical Hospital No. 1 in Nizhny Novgorod, Russia, in 2021–2024.

Study participants

The study included patients with atopic asthma aged 8 to 17 years who were receiving treatment for this disease. Family history related to atopy (asthma, allergic rhinitis, conjunctivitis, atopic dermatitis, urticaria) was assessed. Sensitization to major airborne allergens (house dust mite, cat, dog, and pollen allergens) was investigated using in vivo (prick tests) or in vitro (specific IgE determination) methods.

The criteria for inclusion in the study were:

1. diagnosis of BA established in accordance with applicable international consensus documents (GINA, 2016–2021),
2. patients' age from 8 to 17 years.

The criteria for exclusion were:

1. patients with BMI higher than +2.5Z,
2. presence of acute infectious diseases and fever,

3. presence of diabetes mellitus, autoimmune disorders, primary immunodeficiencies, oncological diseases, atopic dermatitis, parasitic diseases,
4. severe course of BA [1],
5. systemic use of glucocorticoids,
6. use of nonsteroidal anti-inflammatory drugs, ACE inhibitors, drugs used to treat epilepsy.

Data sources

Anthropometric indicators

All patients were assessed for basic anthropometric parameters. All measurements were taken without shoes, outer clothing, or headwear. Anthropometric parameters (height, body weight, and BMI) were assessed using tables developed by the WHO, considering the patients' gender and age. (<https://www.who.int/tools/child-growth-standards>).

BMI calculation: $BMI = \text{body weight (kg)} / \text{height (m)}^2$

Based on BMI assessment data in this study, children were divided into two groups:

Group 1 — underweight and normal weight (BMI values from $-2Z$ to $+1Z$),

Group 2 — excessive body weight and obesity (BMI values above $+1Z$),

Spirometry

Spirometry tests were performed using a MasterScreen pneumospirometer (Jaeger, Germany). The following parameters were evaluated when analyzing spirometry data:

FVC (l) — forced vital capacity, reflects lung volume;

FEV₁ (L/s) — forced expiratory volume in 1 second;

FEV₁/FVC — an index that is the main parameter of spirometry for diagnosing obstructive disorders.

Spirometry data were measured in absolute values and the FEV₁/FVC ratio was calculated.

The FEV₁/FVC z-score was used to diagnose obstructive disorders, with z-score values < -1.645 [11].

In addition, z FVC, z FEV₁ and z FEV₁/FVC c were calculated using the Global Initiative for Chronic Obstructive Lung Disease calculator (<http://gli-calculator.ersnet.org/index.html>), developed with the support of the European Respiratory Society (ERS, <https://www.ersnet.org>).

IL-18 determination

Serum interleukin levels were determined using Interleukin-18-IFA-Best test systems manufactured

Table 1. **Clinical characteristics of patients, spirometric parameters (authors' table)**
 Таблица 1. **Клиническая характеристика пациентов, спирометрические параметры (табл. автора)**

Parameters	Underweight and normal weight (N = 50)	Excess body weight and obesity (N = 35)	Value p
Age, years	13,5 [10,0; 15,0]	13,0 [11,0; 16,0]	0,865
Boys, n = 66	76,0 % (38/50)	80,0 % (28/35)	0,669
z Height	0,30 [-0,45; 0,97]	1,21 [0,58; 1,84]	<0,001
z BMI	-0,09 [-0,43; 0,53]	1,40 [1,22; 1,92]	<0,001
GS %, %	18,18±7,83	27,26±8,15	<0,001
z FVC	0,96±1,26	1,44±1,01	0,032
z FEV1/FVC	-1,14±1,41	-1,56±0,95	0,075
IL-18, pg/ml	208,0 [134,0; 293,0]	251,0 [207,0; 346,0]	0,012

by Vector-Best JSC. Russia, on the ALISEI-QS automated immunoassay analyzer, RADIM GROUP, Italy. The sensitivity of serum IL-18 detection was 0.5 pg/ml, with a range of 0–800 pg/ml.

Statistical analysis

Statistical analysis was performed using Statgraphics Centurion v.16. Quantitative indicators were assessed for compliance with normal distribution using the Shapiro-Wilk test (for fewer than 50 subjects) or the Kolmogorov-Smirnov test (for more than 50 subjects), as well as asymmetry and excess indicators. The data are presented as Me [Q₁; Q₃], where Me is the median, [Q₁; Q₃] is the 1st and 3rd quartiles in the case of abnormal distribution of values, and as M±σ, where M is the mean value, σ is the standard deviation in the case of normal distribution. The Mann-Whitney test was used to compare quantitative variables in two independent groups. Differences between two dependent groups were determined using the Wilcoxon W test. Correlation analysis was performed for normally distributed variables using Pearson's correlation coefficient, and for non-normally distributed variables using Spearman's rank correlation coefficient. Categorical data were described using absolute values and percentages. Differences were assessed using Pearson's χ^2 test. If the

number of expected observations in any of the cells of the four-field table was less than 10, Fisher's exact test was used to assess the significance level of the differences. Differences were considered statistically significant at $p < 0.05$.

The study was a pilot study, so no sample size calculation was performed. Only patients who had no gaps in the data from previous studies were included in the study.

RESULTS

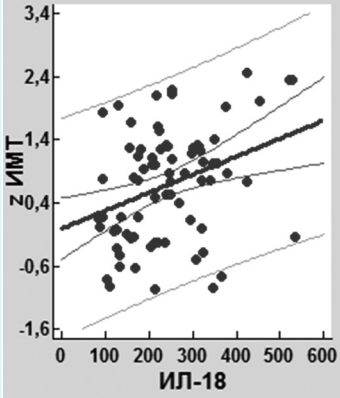
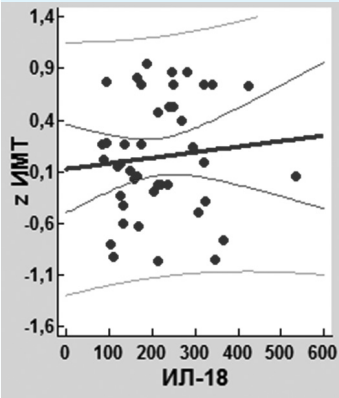
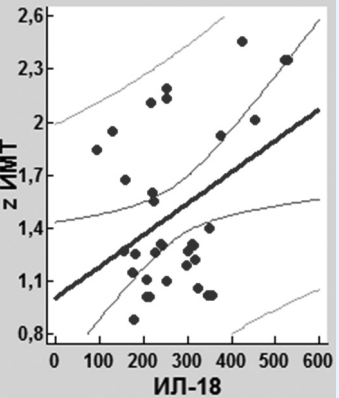
Patients with “low/normal body weight” and “overweight/obesity” were comparable in terms of gender and age (Table 1). The parameters z Height and z BMI were statistically significantly higher in patients who were overweight and/or obese, $p < 0.05$. z FEV1 values were statistically significantly higher, $p = 0.032$, and z FEV1/ FEV1 ratios were lower in the group of patients who were overweight and obese; the differences were of a trend nature, $p = 0.075$. Serum IL-18 levels were statistically significantly higher in the group of patients with overweight and obesity, $p = 0.012$, with individual values not exceeding the threshold values (800 pg/ml).

In study participants with low and normal body weight, serum IL-18 levels did not differ significantly ($p = 0.898$) between patients with and without ob-

Table 2. **IL-18 level of study participants, depending on the presence or absence of obstructive disorders (authors' table)**
 Таблица 2. **Уровень ИЛ-18 участников исследования в зависимости от наличия или отсутствия обструктивных нарушений (табл. автора)**

	All (n = 85)	Without obstructive disorders (n = 36)	With obstructive disorders (n = 49)	Value p
Underweight and normal weight (N = 50)	208,0 [134,0; 293,0]	204,0 [134,0; 304,0]	212,0 [148,0; 250,0]	0,898
Excess body weight and obesity (N = 35)	247,0 [207,0; 334,5]	242,0 [194,5; 313,0]	349,0 [176,0; 452,0]	0,046
All (N = 85)	223,0 [164,0; 311,0]	223,0 [163,0; 307,0]	227,5 [171,0; 352,5]	0,048
Value p	0,012	0,282	0,021	

Table 3. Correlations between the level of IL-18 and z BMI. The data is presented in the form of R, p (authors' table)
Таблица 3. Корреляционные взаимосвязи между уровнем ИЛ-18 и z ИМТ. Данные представлены в виде R, p (табл. автора)

Parameters	All (N = 85)	Underweight and normal weight (N = 50)	Excess body weight and obesity (N = 35)
z BMI	 0,32; 0,004	 0,09; 0,545	 0,34; 0,047

structive disorders (Table 2). In the overweight and obese group, IL-18 levels were statistically significantly higher in patients with obstructive disorders than in patients without them, $p = 0.046$.

In patients without bronchial obstruction, IL-18 levels were comparable in patients with different body weights. In patients with obstructive disorders, IL-18 levels were higher in the group of overweight and obese patients, $p = 0.021$.

Positive correlations were found between IL-18 and z BMI in the general group and in the group of participants who were overweight and obese, $R = 0.32$, $p = 0.004$, $R = 0.34$, $p = 0.047$, respectively. No such correlations were found in the group with low and normal body weight.

DISCUSSION

This study is the first to examine the serum IL-18 content in children and adolescents with asthma and its correlation with the patients' body mass index and the presence of obstructive disorders. The statistically significant higher serum IL-18 levels in patients with asthma combined with overweight and obesity, compared to patients with asthma who are underweight or of normal weight (251.0 [207.0; 346.0] pg/mL versus 208.0 [134.0; 293.0] pg/mL, $p = 0.012$) is likely to reflect systemic low-intensity inflammation

generated by excess adipose tissue. This is confirmed by the presence of a statistically significant direct correlation between serum IL-18 levels and z BMI, which was $R = 0.32$, $p = 0.004$ in the general group and $R = 0.34$, $p = 0.047$ in the overweight and obese group. Elevated IL-18 levels were noted in the work of M. Bantula et al. [10], which is consistent with our data.

The level of IL-18 depended on the presence or absence of obstructive disorders, which were diagnosed using spirometry, namely, a z-score of FEV1/FVC less than -1.645 .

In patients with obstructive disorders, IL-18 levels were statistically significantly higher in the group of overweight and obese children. In the absence of obstructive disorders in patients, no statistically significant differences in IL-18 levels were found in children with low/normal body weight and in children who were overweight or obese. This may indicate the effect of non-T2-dependent inflammatory mechanisms on the formation of an obstructive pattern in overweight and obese children. We found no literature data on the role of IL-18 and its connection with lung function in asthma combined with excessive body mass and obesity in children. However, several studies suggest that in adult patients, IL-18 may be the basis for lower FEV1 [12, 13].

CONCLUSION

Thus, patients with asthma and overweight or obesity, but not patients with low or normal body weight, have higher levels of IL-18 in the presence

of bronchial obstruction. This may indicate the involvement of this interleukin in the pathogenesis of bronchial obstruction in patients who are overweight or obese.

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THE AUTHOR' CONTRIBUTION TO THE WORK

Regina N. Khramova — conceptualization, investigation, visualization, writing — review & editing.

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Храмова Р. Н. — разработка концепции, проведение исследования, работа с данными, подготовка текста — оценка и редактирование.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Privolzhsky Research Medical University (Protocol No. 13 dated 10.10.2016). All participants and all primary care providers gave written informed consent.

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