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The cytokine profile in obesity and asthma in children

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ABSTRACT

Background. Childhood obesity is one of the pressing problems in modern healthcare, since it is associated with a high risk of non-communicable diseases, such as bronchial asthma (BA).

The aim. To determine the features of cytokine profiles in children with and without BA, depending on body weight and visceral fat area.

Materials and methods. At the first stage, 506 Tomsk schoolchildren underwent anthropometry with the calculation of the body mass index (BMI) and measurement of the visceral fat area (VFA) using the InBody 770 analyzer. Fifty-one (51) children from the first stage were included in the second clinical and diagnostic stage. The children were divided into four clinical groups: "Obesity" (n = 17), "Visceral Obesity" (n = 7), "Asthma" (n = 15), and "Healthy Children" (n = 12). In all study participants, the levels of interleukin (IL)-6, IL-8, IL-4, IL-10, and immunoglobulin (Ig) E in the blood serum were determined by the multiplex assay (MagPix and Luminex 200 c analyzers). Statistical data analysis was carried out using the Statistica 10.0 software package and the 4.2.2 version of R.

Results. The levels of IL-10 in the "Asthma" ($p < 0.006$) and "Obesity" ($p < 0.008$) groups were significantly higher than in the "Visceral Obesity" group. Significantly higher levels of IL-8 were found in patients with asthma ($p < 0.003$) and obesity ($p < 0.003$) compared to the "Visceral Obesity" group. Higher concentrations of IL-6 were found in the "Asthma" ($p < 0.001$) and "Obesity" ($p < 0.028$) groups compared to the "Visceral Obesity" group.

Conclusion. Similar upward changes in IL-6, IL-8, and IL-10 in children with asthma and obesity without a history of asthma may explain the contribution of obesity to a risk of asthma in children, possibly through excessive production of these proinflammatory cytokines that contribute to the implementation of Th2-mediated allergic inflammation.

Keywords: asthma, obesity, visceral obesity, inflammation, cytokines

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Conformity with the principles of ethics. A legally authorized representative of every child signed an informed consent to carrying out of the procedures. The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 8459/2 of 28.10.2020).

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Цитокиновый профиль при ожирении и бронхиальной астме у детей

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РЕЗЮМЕ

Введение. Детское ожирение является одной из актуальных проблем современного здравоохранения, поскольку связано с высоким риском возникновения хронических неинфекционных заболеваний, таких как бронхиальная астма (БА).

Цель исследования – определение особенности цитокиновых профилей у детей с диагностированной БА и без нее в зависимости от массы тела и площади висцерального жира.

Материалы и методы. На первом этапе 506 школьникам г. Томска выполнена антропометрия с расчетом индекса массы тела, измерение площади висцеральной жировой ткани на аппарате Inbody 770. Во второй клинико-диагностический этап включен 51 ребенок из первого этапа. Сформированы четыре клинические группы: «ожирение» (n = 17), «висцеральное ожирение» (n = 7), «бронхиальная астма» (n = 15) и здоровые дети (n = 12). Всем участникам определен уровень интерлейкина (IL) 6, 8, 4, 10 и иммуноглобулина (Ig) E в сыворотке крови путем мультиплексного анализа (анализаторы MagPix и Luminex 200 с). Статистический анализ данных проведен с помощью пакета программы Statistica for Windows 10.0, а также с использованием языка R (версия 4.2.2).

Результаты. Уровень IL-10 в группах «бронхиальная астма» (p < 0,006) и «ожирение» (p <0,008) был достоверно более высоким по сравнению с группой «висцеральное ожирение». При оценке IL-8 установлен достоверно более высокий уровень у больных БА (p < 0,003) и ожирением (p < 0,003) чем при висцеральном ожирении. Более высокие концентрации IL-6 выявлены в группах «бронхиальная астма» (p < 0,001) и «ожирение» (p < 0,028) по сравнению с группой «висцеральное ожирение».

Заключение. Схожие изменения IL-6, IL-8, IL-10 в сторону их повышения у детей, страдающих бронхиальной астмой и ожирением без анамнеза астмы, могут объяснять вклад ожирения как фактора риска при астме у детей, возможно, через избыточную продукцию указанных провоспалительных цитокинов, способствующих реализации аллергического Th2-опосредованного воспаления.

Ключевые слова: бронхиальная астма, ожирение, висцеральное ожирение, воспаление, цитокины

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INTRODUCTION

Obesity in childhood and adolescence is one of the pressing issues of modern healthcare, as it is associated with a high risk of chronic non-communicable diseases, such as asthma, arterial hypertension, and type 2 diabetes mellitus at an older age [1–4]. According to the World Health Organization (WHO), in 2020, obesity was registered in 4.4 million (7.9%) children under the age of 5 years in the European region [5].

Furthermore, this report states that every eighth child (11.6%) aged 5–9 years is obese, and every third child (29.5%) is overweight [5]. A study conducted in eight (8) federal districts of Russia in 2017 that included 2,000 children showed that the incidence of obesity in boys aged 11 and 15 years was 18.6 and 10%, respectively. In girls aged 11 and 15 years, it was 9.2 and 3.6%, respectively [6].

Currently, special attention is paid to patients with excess visceral adipose tissue (VAT) who have a normal body mass index (BMI) [7]. Iu.G. Samoilova et al. in their work found that the prevalence of visceral obesity in children under the age of 10 years (n = 625) was 2% in girls and 1.6% in boys, and in the group older than 10 years (n = 1,314) – 6.7% in girls and 8.5% in boys [8].

Numerous studies have shown that obesity or overweight is associated with the development of asthma in children [9–11]. At the same time, patients with asthma and obesity had a worse response to the use of budesonide in relation to lung function and also more often required hospitalization for asthma [12, 13]. Additionally, the results of some works indicate a possible role of excess VAT in the development of systemic inflammation and an increase in the subsequent risk of chronic non-communicable diseases, such as asthma [2, 14, 15]. In particular, the mechanism of participation of M1 macrophages, which promote the secretion of non-T2 cytokines (TNFα, IL-17A, IL-21, IFNγ, TGF-β1, IL-6) by activated Th1 and / or Th17 lymphocytes in the adipose tissue, with subsequent accumulation of neutrophils in the target tissues is discussed [15–17].

The work by H.A. Periyalil et al. showed that in adult patients with obesity and asthma, the number of M1 macrophages in the VAT correlates with BMI [18]. On the other hand, studies demonstrate the development of chronic inflammation involving VAT and subcutaneous adipose tissue (SAT) [19].

In general, current research results are miscellaneous and do not provide an insight into the contribution of inflammation initiated by visceral or subcutaneous obesity to the risk of developing asthma in children.

The aim of the study was to determine the features of the cytokine profile in children with diagnosed asthma and those without it, depending on body weight and visceral fat area.

MATERIALS AND METHODS

The present study was carried out in two stages. The first epidemiological stage was a part of a multicenter, prospective epidemiological study "Prevention of Obesity in Children and Adolescents (Clinical, Metabolic, Diagnostic, and Rehabilitation Aspects)" carried out from October 2020 to June 2021 in four schools in Tomsk (approved by the Ethics Committee at Siberian State Medical University, Protocol No. 8459/2 of 28.10.2020). As part of this stage, 506 schoolchildren aged 7–12 years were continuously included in the study, with the exception of children with monogenic obesity, type 1 and 2 diabetes mellitus, and severe or unstable somatic symptom disorder. Before carrying out the prescribed procedures, the legal representative of the child signed an informed consent.

In this group, a set of studies was performed, including measurement of anthropometric parameters (height, weight) in light clothes and without shoes, using scales installed in the InBody 770 analyzer (accuracy 0.1 kg) and the MSK-233 medical stadiometer (accuracy up to 0.1 cm). The Standard Deviation Score for BMI was calculated using the WHO Anthro Plus; a bioimpedance analysis with determination of the visceral fate area was performed using the InBody 770 analyzer.

At the second clinical diagnostic stage, a case-control study was conducted, and all participants from the first phase were offered the opportunity to continue participating in the study. After the first stage, the children were divided into four clinical groups: group 1 consisted of patients with obesity (n = 17); group 2 consisted of patients with normal SDS BMI and visceral obesity according to the bioimpedance analysis (n = 7); group 3 included patients with asthma without excess VAT and obesity (n = 15); and group 4 encompassed healthy children (n = 12). Patients with asthma were recruited from the clinical database of the Children's Clinic of Siberian State Medical University. The children were examined for the serum levels of cytokines (IL-6, IL-8, IL-4, IL-10) on the Magpix and Luminex 200 multiplex analyzers (Luminex Corp., USA) at the "Medical Genomics" Center for Collective Use (Tomsk NRMC).

Statistical data processing was carried out using the Statistica for Windows 10.0 software package. Descriptive statistics were used to process the results of the study. Normality of data distribution was checked using the Shapiro – Wilk test. Normally distributed quantitative data were presented as the arithmetic mean and standard deviation $M \pm SD$. For non-normal distributions, the median and the interquartile range $Me\ (Q_1; Q_3)$ were calculated. The differences in paraclinical parameters between the groups were assessed

using the Mann – Whitney – Wilcoxon test (for quantitative variables). The differences were considered statistically significant at $p < 0.05$.

The statistical analysis was also carried out using the R language (version 4.2.2). Prior to the analysis, cytokine values were normalized using the rank normalization method and converted to units of standard deviation. Then, the sample was analyzed for multivariate outliers. To assess the contribution of the patients' condition and their anthropometric parameters to the variability of cytokine concentration, we used the multivariate analysis of variance for distance matrices with permutations (the adonis2 function in the R vegan package). To do this, we calculated the distance matrix between the cytokine concentrations in patients in Euclidean space (the vegdist function in the R vegan package) and then applied adonis2 with 9999 permutations and calculated the marginal effects for all variables. The model included age, BMI, gender, grouping by clinical parameters, and VAT / VFA. The pairwise.adonis function was used to search for pairwise differences between the groups of patients. For multiple comparisons, the false discovery rate (FDR) was used for *p* values.

RESULTS

The article shows the results of the second clinical diagnostic stage. Fifty-one (51) children were included in the clinical diagnostic phase of the study, 31 of whom (58%) were boys and 20 (36%) were girls. The mean age was 9.3 (9; 10) years. The main anthropometric, gender, and age characteristics, as well as the results of the bioimpedance analysis of kinetic groups are shown in Table 1.

The allergic nature of the diseases was confirmed in all patients of the "Asthma" group by the results of the study of IgE and IL-4, which amounted to 450 IU / ml (151.6; 500) and 76.1 pg / ml (2.61; 428.7), respectively.

The results of assessing the levels of proinflammatory cytokines IL-6, IL-8, and IL-10 are presented in Table 2.

Table 1

Anthropometric, gender, and age characteristics and results of the bioimpedance analysis of the clinical groups

Group	Height, cm, $M \pm SD$	BMI, $M \pm SD$	VFA, cm^2 $M \pm SD$	Gender		Age, years, $Me\ (Q_1; Q_3)$
				boys	girls	
Group 1, $n = 17$	142.3 ± 6,3	24.3 ± 4.11	99.1 ± 48.3	10	7	9 (9; 10)
Group 2, $n = 7$	144.5 ± 4.5	17.2 ± 1.13	46.9 ± 5.7	2	5	10 (9;10)
Group 3, $n = 15$	139.1 ± 6.3	15.4 ± 1.03	24 ± 7.6	11	4	9 (8;10)
Group 4, $n = 12$	138.0 ± 5.9	16.4 ± 0.6	24.7 ± 9.2	8	4	9 (9;10)

Table 2

Variability of IL-6, IL-8, and IL-10 levels in the clinical groups, pg / ml $Me\ (Q_1; Q_3)$

Parameter	Group 1, $n = 17$	Group 2, $n = 7$	Group 3, $n = 15$	Group 4, $n = 12$
IL-10	1.83 (1.10; 3.72)[2]	0.92 (0.43; 1.14)[1, 2]	2.1 (1.15; 3.79)[1]	1.26 (1.09; 2.05)
IL-8	8.9 (5.48; 14.25)[2]	4.36 (2.23; 4.76)[1, 2, 3]	9.6 (6.43; 29.3)[1]	8.9 (7.5; 11.01)[3]
IL-6	1.3 (0.46; 5.39)[2]	0.46 (0.25; 0.46)[1, 2, 3]	5.3 (1.02; 20.6)[1, 4]	0.48 (0.46; 1.49)[3, 4]

Note: significant differences ($p < 0.05$) between the groups: [1] "Asthma" and "Visceral obesity", [2] "Obesity" and "Visceral obesity", [3] "Visceral obesity" and "Healthy Children", [4] "Asthma" and "Healthy Children" (Mann – Whitney *U*-test).

The IL-10 level in the "Asthma" ($p < 0.006$) and "Obesity" ($p < 0.008$) groups was significantly higher than in the "Visceral Obesity" group (Table 2). When evaluating proinflammatory IL-8, significantly higher levels were found in patients with asthma ($p < 0.003$) and obesity ($p < 0.003$) than in patients with visceral obesity. The study of proinflammatory IL-6 demonstrated its higher content in the "Asthma" ($p < 0.001$) and "Obesity" ($p < 0.028$) groups compared to the "Visceral Obesity" group (Table 2).

At the next stage, the overall cytokine profile was assessed using a multivariate analysis of variance, which included such characteristics as age, BMI, gender, clinical group, and VFA. Table 3 shows the correlation between these characteristics and the overall cytokine profile.

Table 3

Correlation between patients' characteristics and the overall cytokine profile (IL-6, IL-8, IL-4, IL-10)

Parameter	R^2	p
Age	0.015	0.353
Gender	0.033	0.059
BMI	0.045	0.018
VFA	0.045	0.019
Clinical groups	0.110	0.028

Note: R^2 – coefficient of determination (here and in Table 4).

The results of the nonparametric analysis of variance showed that the "Clinical groups" parameter explained 11% variability in the cytokine levels ($R^2 = 0.110$, $p = 0.028$), 4% variability in the BMI ($R^2 = 0.045$, $p = 0.018$), and 4% variability in VFA ($R^2 = 0.045$, $p = 0.019$).

After that, the intergroup differences in the overall cytokine profile were analyzed using the pairwise. adonis function (Table 4).

Table 4

Correlation between the cytokine profile and the clinical groups

Clinical groups	R^2	p	p-adjusted
Asthma vs Visceral Obesity	0.247	0.0021	0.0105
Asthma vs Obesity	0.049	0.169	0.241
Asthma vs Healthy Children	0.100	0.031	0.078
Visceral Obesity vs Obesity	0.140	0.007	0.023
Visceral Obesity vs Healthy Children	0.177	0.001	0.005
Obesity vs Healthy Children	0.029	0.545	0.681

Note: achieved significance level with the FDR – p-adjusted.

During the pairwise comparisons of the clinical groups in the overall cytokine concentration, significant differences were found between the following groups: "Asthma" and "Visceral Obesity" ($R^2 = 0.247$, $p = 0.002$); "Visceral Obesity" and "Obesity" ($R^2 = 0.140$, $p = 0.007$); and "Visceral Obesity" and "Healthy Children" ($R^2 = 0.177$, $p = 0.001$). However, no significant differences were found between the "Asthma" and "Obesity" groups (Table 4).

DISCUSSION

Obesity and asthma are included in the group of chronic non-communicable diseases in children and adolescents [20]. Researchers are actively discussing the role of obesity and visceral obesity as possible risk factors for the development of asthma, as well as concomitant diseases that aggravate the course of asthma [4, 20–22]. The results of this study indicate similar upward changes in some non-T2 cytokines (IL-6, IL-8, IL-10) in asthmatic children and obese children without asthma. It is the unidirectionality of proinflammatory changes that can be the fundamental basis for the realization of the risk of developing asthma in obese children. These changes were not confirmed in the group of patients with visceral obesity without an increase in BMI, which may indicate lower proinflammatory activity of VAT in these patients in relation to the production of the studied cytokines and / or the significance of high BMI in the pathogenesis of these abnormalities.

In terms of heterogeneity of clinical manifestations and differences in the immune response, two main endotypes of asthma are distinguished [20]. The T2 endotype (T2-high), which is mediated predominantly through the activity of Th2 lymphocytes, is the main mechanism of childhood allergic asthma, characterized by eosinophilic inflammation and secretion of T2 cytokines (IL-4, -5, -9, and -13) [23, 24]. Indeed, patients with asthma had high levels of IgE and IL-4, reflecting the activity of Th2 inflammation. Along with the basic allergic mechanism, high levels of non-Th2 cytokines (IL-6, IL-8, and IL-10) were also registered in the patients with asthma during the study. The overall cytokine profile in asthma during the multivariate analysis of variance did not show significant differences with the "Obesity" group, but significantly differed from the "Visceral Obesity" group due to lower levels of the studied cytokines.

It is well-known that IL-6 is involved in the development of neutrophilic inflammation [25]. Studies also indicate that the involvement of this cytokine in the development of inflammation in allergic asthma is associated with the ability to regulate differentiation of naive CD4 T lymphocytes to Th2 cells through synthesis of IL-4 [26, 27].

IL-8 shows high levels in children with asthma. This cytokine has chemoattractant activity, mainly in relation to neutrophil chemotaxis in the focus of inflammation [14, 28]. Meanwhile, M. Hodeib et al. (2021) found a correlation between the IL-8 concentration and the IgE level ($r = 0.789$, $p < 0.001$) in the blood serum [29].

On the one hand, published data confirm the role of IL-10 in the regulation of allergic inflammation and IgE synthesis [30, 31]. On the other hand, IL-10 promotes the activation of M2 macrophages in the adipose tissue and exerts a direct effect on adipocytes, reducing their proinflammatory activity, which may explain high levels of this cytokine in obese patients [32].

CONCLUSION

Therefore, the non-Th2 cytokines studied in this work (IL-6, IL-8, IL-10), which are well-known participants of systemic inflammation in obesity, are also involved in the development of inflammation in allergic asthma. Altogether, this similarity of mechanisms may underlie the contribution of obesity as a risk factor for asthma in children, possibly through overproduction of these proinflammatory cytokines that promote allergic Th2-mediated inflammation.

As for visceral obesity, the results of this study do not allow to confirm the independent role of VAT in the implementation of systemic inflammation in the context of the studied proinflammatory cytokines.

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