ISSN 2500-1175 (PRINT)
ISSN 2712-7958 (ONLINE)

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

https://adair.elpub.ru/

TOPICS IN THE ISSUE:

ТОМ 23, ВЫПУСК 2
ISSUE: ISSUE 2

ИЮНЬ 2025
JUNE 2025

Ассоциация детских аллергологов и иммунологов России
Наш подписной индекс: 47432

JUNE 2025

ISSN 2712-7958 online | **Allergologiya i immunologiya v pediatrii** | **ISSN 2500-1175** print

ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

Volume 23, Issue 2, *June 2025*

Allergology and Immunology in Pediatrics is the official journal of the Association of Pediatric Allergologists and Immunologists of Russia. The journal has been published since 2003. All position papers of the Association are published as journal articles and are available to specialists for free. The journal publishes original research and thematic review articles by Russian and international scientists. Special attention is given to the regional and geographic features of the occurrence and prevalence of allergic diseases among Russian children. Among the authors are key leaders from leading major regional universities in the Russian Federation. Our goal is to provide open access to up-to-date scientific information and research results for practical pediatricians, allergists, immunologists, dermatologists, and research scientists. Since 2023, we have become bilingual, offering both Russian and English versions of our journal, which aligns with the principles of international scientific collaboration. We provide doctors and scientists, including allergists, pediatricians, dermatologists, and immunologists, with the opportunity to engage in open scientific discussions and publish clinical cases and original articles. These articles focus on the study of the causes and treatment of allergic diseases, as well as the formation of the immune response in both normal and diseased conditions.

OFFICIAL JOURNAL OF THE ASSOCIATION OF PEDIATRIC ALLERGISTS AND IMMUNOLOGISTS OF RUSSIA (APAIR)

Founder and publisher of the journal: Association of Pediatric Allergists and Immunologists of Russia, 6 Ostrovityanova Str., Moscow, 117513, Russian Federation, phone: +7 495 225 71 04, www.adair.ru • adair@adair.ru

With support of
Kazan State Medical University
Samara State Medical University
Academy of postgraduate education under FSBU FSCC of FMBA of Russia

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The journal «Allergology and Immunology in Pediatrics» is registered with the Ministry of Press, Broadcasting and Mass Communications Russian Federation. Registration number: PI No. 77-17742 dated March 9, 2004. The journal was printed in the printing house of JSC «PFOP», Russia, 142100, Podolsk, Revolutionary avenue, 80/42. Edition: 1000 copies. The issue is signed for publication: June 20, 2025. The journal materials are distributed under a Creative Commons license.
The journal is published 4 times a year. A subscription to the journal «Allergology and Immunology in Pediatrics» can be issued at any post office in Russia.
The subscription index of the publication is 47432. The price is free.

ISSN 2712-7958 online | **Allergologiya i immunologiya v pediatrii** | **ISSN 2500-1175** print

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

Том 23, выпуск 2, *июнь 2025*

Аллергология и иммунология в педиатрии – официальный журнал Ассоциации детских аллергологов и иммунологов России. Журнал издается с 2003 года. Все позиционные документы Ассоциации выходят в виде статей журнала и доступны свободно для специалистов. В журнале публикуются оригинальные исследования и тематические обзорные статьи российских и зарубежных ученых. Особое внимание уделено региональным и географическим особенностям возникновения и распространённости аллергических заболеваний у детей России. В составе авторов ключевые лидеры ведущих крупных региональных университетов РФ. Нашими целями является обеспечение предоставления открытого доступа к современной научной информации и результатам научных исследований практическим педиатрам, аллергологам – иммунологам, дерматологам и ученым – исследователям. С 2023 года журнал стал двуязычным (русский и английский), что соответствует принципам международного научного сотрудничества. Мы предоставляем врачам и ученым (аллергологам, педиатрам, дерматологам, иммунологам) возможность для открытых научных дискуссий и публикации клинических случаев и оригинальных статей, обзоров, связанных с изучением причин и методов лечения аллергических болезней, формирования иммунного ответа в нормальных условиях и при заболевании.

ОФИЦИАЛЬНЫЙ ПЕЧАТНЫЙ ОРГАН АССОЦИАЦИИ ДЕТСКИХ АЛЛЕРГОЛОГОВ И ИММУНОЛОГОВ РОССИИ (АДАИР)

Учредитель и издатель: Общероссийская общественная организация «Ассоциация детских аллергологов и иммунологов России», Россия, 117513, г. Москва, ул. Островитянова, д. 6, тел.: +7 495 225 71 04, www.adair.ru • adair@adair.ru

При поддержке ФГБОУ ВО «Казанский государственный медицинский университет» Минздрава России
ФГБОУ ВО «Самарский государственный медицинский университет» Минздрава России
Академия постдипломного образования ФГБУ ФНКЦ ФМБА России

Редакция журнала «Аллергология и Иммунология в Педиатрии» 117513, г. Москва, ул. Островитянова, д. 6, офис 9, Тел.: 8(495) 225-71-04
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Решением Высшей аттестационной комиссии (ВАК) Министерства образования и науки РФ журнал «Аллергология и иммунология в педиатрии» включен в Перечень ведущих рецензируемых научных журналов и изданий, выпускаемых в Российской Федерации, в которых рекомендована публикация основных результатов диссертационных исследований на соискание ученых степеней доктора и кандидата наук по специальностям: 3.1.21. Педиатрия (медицинские науки), 3.1.23. Дерматовенерология (медицинские науки), 3.2.7. Аллергология и иммунология (биологические и медицинские науки). С 1.01.2024 присвоен К2 сроком на 3 года.

Журнал «Аллергология и иммунология в педиатрии» зарегистрирован в Министерстве по делам печати, телерадиовещания и средств массовых коммуникаций РФ. Регистрационный номер: ПИ №77-17742 от 9.03.2004 г. Журнал отпечатан в типографии ОАО «ПФОП», Россия, 142100, г. Подольск, Революционный проспект, д. 80/42. Тираж: 1000 экз. Номер подписан в печать: 20.06.2025 г. Материалы журнала распространяются под лицензией Creative Commons.
Журнал выходит 4 раза в год. Подписку на журнал «Аллергология и иммунология в педиатрии» можно оформить в любом отделении связи на территории России. Подписной индекс издания 47432. Цена свободная.

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REV — обзорная статья

https://doi.org/10.53529/2500-1175-2025-2-4-14

Date of receipt: 01.11.2024
Date of acceptance: 02.04.2025
Date of publication: 17.06.2025

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Abstract

Introduction. Tryptase, a mast cell-derived protease, plays a significant role in the diagnosis and pathogenesis of allergic and inflammatory diseases. The baseline serum tryptase level is used as a biomarker for the diagnosis of conditions associated with mast cell activation, which may be accompanied by severe allergic reactions and anaphylaxis. Studying tryptase isoforms, along with their structural and functional variations, aids in understanding genetic predisposition and the mechanisms underlying inflammatory diseases such as bronchial asthma and chronic inflammation.

Materials and Methods. A detailed investigation of the structure and function of various tryptase isoforms was conducted. Biochemical properties human tryptase isoforms were examined. The analysis included the study of the genes TPSAB1, TPSB2, TPSG1, and TPSD1, which encode different forms of tryptase, and the assessment of their activity. Tryptase secretion has been investigated, along with various factors influencing its release.

Results. Tryptase, a mast cell-derived enzyme, is represented by four major isoforms—α, β, γ, and δ. Among the secreted isoforms, α- and β-tryptases are the most prominent, β-tryptase exhibits the highest catalytic activity, whereas α-tryptase demonstrates limited enzymatic function. The tryptase genes are located on chromosome 16 and show a high degree of homology. Key genes TPSAB1 and TPSB2 encode active forms of tryptase, and an increased number of TPSAB1 copies leads to elevated baseline tryptase levels, heightening the risk of allergic reactions. Tryptase plays a role in inflammatory and allergic processes, including mast cell degranulation, affecting vascular permeability and leukocyte recruitment.

Conclusion. The collected data on the secretion and functions of tryptase produced by mast cells suggest that it can be regarded as a multifunctional mediator, acting through specific molecular and cellular mechanisms. Tryptase is critically involved in the pathogenesis of inflammatory processes and allergic responses across multiple organs and systems, including the respiratory tract and the skin. Understanding the biochemical characteristics and genetic features of tryptase isoforms opens new opportunities for the development of diagnostic and therapeutic approaches for high-impact allergic diseases.

Keywords: tryptase, mast cells, secretion, enzyme, marker

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

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For citation: Tarasova N. E., Lebedenko A.A., Semernik O. E., Dobaeva N. V., Skosar V. O., Haygetyan N. U., Krivokhlyabov I. P., Shkilnyuk S. P. Genetic, morphological and functional characteristics of human tryptase. *Allergology and Immunology in Pediatrics*. 2025; 23 (2): 4–14. https://doi.org/10.53529/2500-1175-2025-2-4-14

Генетические, морфологические и функциональные особенности триптазы человека

https://doi.org/10.53529/2500-1175-2025-2-4-14

УДК 612.017.1:577.156.3:575.191:572.7]-053.2
Дата поступления: 01.11.2024
Дата принятия: 02.04.2025
Дата публикации: 17.06.2025

Тарасова Н. Е., Лебеденко А. А., Семерник О. Е., Добаева Н. В., Скосарь В. О., Хейгетян Н. Ю., Кривохлябов И. П., Шкильнюк С. П.

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Аннотация

Актуальность. Триптаза, фермент тучных клеток, играет значимую роль в диагностике и патогенезе аллергических и воспалительных заболеваний. Базовый уровень триптазы в сыворотке используется как индикатор для диагностики заболеваний, сопровождающихся активацией тучных клеток, которые могут сопровождаться тяжелыми аллергическими реакциями и анафилаксией. Изучение изоформ триптазы, их структурных и функциональных вариаций, помогает понять генетическую предрасположенность и механизмы воспалительных заболеваний, таких как бронхиальная астма и хроническое воспаление.

Материалы и методы. Проведено детальное исследование структуры и функций различных изоформ триптазы. Изучены биохимические особенности различных изоформ триптазы человека. Анализ включал изучение генов TPSAB1, TPSB2, TPSG1 и TPSD1, кодирующих разные формы триптазы, а также оценку их активности. Изучена секреция триптазы, а также факторы, влияющие на ее секрецию.

Результаты. Триптаза, фермент тучных клеток, представлена четырьмя основными изоформами — α, β, γ и δ. Среди них α- и β-триптазы являются секретируемыми, при этом β-триптаза обладает наибольшей каталитической активностью, тогда как α-триптаза имеет низкую ферментативную активность. Гетеротетрамеры α/β обладают уникальной активностью по сравнению с гомотетрамерами β, задействуя молекулы-мишени, неактивные для β-гомотетрамеров, что оказывает влияние на активность тучных клеток. Гены триптазы расположены на хромосоме 16 и имеют высокую степень гомологии. Важные гены TPSAB1 и TPSB2 кодируют активные формы, а увеличение числа копий TPSAB1 приводит к повышению базальных уровней триптазы, увеличивая риск развития аллергических реакций. Триптаза играет роль в воспалительных и аллергических процессах, в том числе в дегрануляции тучных клеток, влияя на сосудистую проницаемость и привлечение лейкоцитов.

Заключение. Собранные данные о секреции и функциях триптазы, продуцируемой тучными клетками, позволяют считать ее многофункциональным медиатором, воздействующим посредством специфических молекулярных и клеточных механизмов. Триптаза играет важную роль в патогенезе воспалительных процессов и аллергических реакций в разнообразных органах и системах, включая респираторную систему и кожу. Понимание биохимических характеристик и генетических особенностей изоформ триптазы открывает возможности для разработки новых методов диагностики и лечения аллергических заболеваний с высокой социальной значимостью.

Ключевые слова: триптаза, тучные клетки, секреция, фермент, маркер

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Тарасова Н. Е., Лебеденко А. А., Семерник О. Е., Добаева Н. В., Скосарь В. О., Хейгетян Н. Ю., Кривохлябов И. П., Шкильнюк С. П. Генетические, морфологические и функциональные особенности триптазы человека. *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 4–14. https://doi.org/10.53529/2500-1175-2025-2-4-14

INTRODUCTION

Tryptases belong to the family of serine proteases of mast cells. In healthy individuals, baseline serum tryptase levels are stable. Baseline serum tryptase concentration is an important diagnostic marker, as its elevation may indicate the presence of diseases associated with mast cell dysfunction and increase the risk of severe allergic reactions. Studies show that even tryptase levels within the normal range may be associated with an increased likelihood of allergic conditions. In acute cases, such as anaphylaxis, tryptase levels rise significantly, reaching peak values. Therefore, it is extremely important to perform sequential peak and baseline measurements of serum tryptase in acute situations, especially during the assessment of anaphylaxis [1].

Tryptases can have different genetic variants, perform different functions, and participate in the development of diseases in different ways. Future research on tryptase requires the improvement of laboratory methods that will allow for a more accurate assessment of its biological functions, participation in pathological processes, and clinical significance.

ISOPHORMS AND STRUCTURE OF HUMAN TRYPTASE

Human tryptases consist of four isoforms, including secreted α- and β-tryptases encoded by the TPSAB1 and/or TPSB2 genes, δ-tryptase encoded by the TPSD1 gene, and membrane-bound γ-tryptase encoded by the TPSG1 gene (Table 1).

Human δ-tryptase has a C-terminal truncation and lacks important substrate-binding residues. Thus, human δ-tryptase is considered a protein with no biological activity.

Tryptase, a mast cell enzyme, is represented by four main isoforms: α, β, γ, and δ. Among them, α- and β-tryptase are secreted, with β-tryptase having the highest catalytic activity, while α-tryptase has low enzymatic activity. In most serine proteases, including β-tryptase, a glycine residue is found at position 216, which is necessary for the proper functioning of the active site. α-tryptase has virtually no catalytic activity, partly due to the replacement of aspartic acid at this position. In α-tryptase, this position is occupied by aspartic acid, which reduces its catalytic ability. In addition, the amino acid substitutions p.G216D and

Table 1. **Biochemical characteristics and enzyme formats of various human tryptase isoforms (author's table)**
Таблица 1. **Биохимические особенности и форматы ферментов различных изоформ триптазы человека (таблица автора)**

Tryptase isoforms	Gene	Activity	Protein-enzyme format
α-tryptase	*TPSAB1*	inactive	Inactive promo number
			Inactive homotetramer
			Active heterotetramer α/β
βI-tryptase	*TPSAB1* или *TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
βII-tryptase	*TPSAB1 или TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
βIII-tryptase	*TPSAB2*	triptych	Inactive promonomer and monomer
			Active tetramer
γ-tryptase	*TPSG1*	triptych	Active; with membrane mounting
δ-tryptase	*TPSD1*	inactive	Truncated; probably monomeric

p.D189K cause changes in segment 214–220, which leads to partial filling of the S1 pocket, the active site region necessary for substrate binding. These structural features prevent substrate access to the active site, which explains the low activity of α-tryptase [2].

β-tryptase has three main isoforms: βI-tryptase, βII-tryptase, and βIII-tryptase. These three isoforms of β-tryptase have more than 95% homology and similar catalytic activity. Among β-tryptases, approximately 23% of people of European descent carry a nonsense variant of βIII-tryptase, resulting from the insertion of a single base pair, which leads to a reading frame shift and a premature stop codon (βIII FS). In the case of expression, the resulting protein will have a large truncation at the C-terminus and will not have an active site [3].

The ratio of active β-tryptase alleles to inactive alleles (including α-tryptase and βIII FS-tryptase) determines the activity of tryptase in mast cell granules. [2].

The genetic basis of frequent and recurrent loss-of-function variants that led to the formation of α-tryptase, truncated βIII FS-tryptase, and δ-tryptase during human evolution, as well as how active and inactive tryptase alleles affect human disease and host defense, is not fully understood at present [2]. α-tryptase does not have a functional active site and does not possess any catalytic activity of its own. However, pairs of α-tryptase with β-tryptase form active α/β-tryptase heterotetramers.

Tryptase is a tetrameric trypsin-like protease with a strictly controlled assembly mechanism. Full-length tryptases contain a propeptide at their N-terminus (protryptase zymogen); cleavage of the propeptide by cathepsins in mast cell granules appears to be necessary for tryptase activation [4]. Mature tryptase monomers (with removed propeptide sequences) form tetramers in the secretory granules of mast cells, which have an acidic pH environment and abundant heparan glycosaminoglycans. Since tryptase monomers have negligible catalytic activity under physiological conditions, tetrameric tryptases are the predominant enzymatically active protease in mast cell granules. Tetramer formation is facilitated under low pH conditions and by binding to heparin glycosaminoglycan. Structural analysis of mature tryptases reveals a toroidal, doughnut-like tetramer comprising protomers that interact with their neighbors at both large and small interfaces. In this tetrameric form, each tryptase protomer serves as a cofactor to stabilize the neighboring tryptase in a catalytically active conformation [5]. Although α-tryptase does not possess any intrinsic catalytic activity, the α-tryptase promoter can stabilize and activate the adjacent β-tryptase in the α/β-tryptase heterotetrameric format. Interestingly, α/β-tryptase heterotetramers are reported to have altered catalytic activity toward certain substrates, such as EMR2 and PAR2 cell surface receptors, compared to β-tryptase homotetramers. In addition, tryptase may have unique effects when interacting with neighboring β-tryptases to regulate the overall catalytic conformations of β-tryptase and/or substrate accessibility [6]. Interactions between promoters within tryptases are stabilized by heparin, which is negatively charged and binds to a large positively charged surface encompassing both small interface surfaces. Since there are no known endogenous inhibitors of tetrameric tryptase, low concentrations of extracellular heparin in the peripheral circulation may serve as a natural mechanism of inactivation. The concentration gradient of heparin from high concentrations inside cells to low concentrations in the extracellular space promotes the gradual dissolution of active tryptase tetramers, i.e., their conversion into inactive forms [7]. A distinctive feature of α-tryptase compared to β-tryptase is its ability to activate independently of heparin, as well as at lower pH values in insufficiently vascularized areas, which is particularly important for tissues with chronic inflammation or in the pathogenesis of bronchial asthma [8].

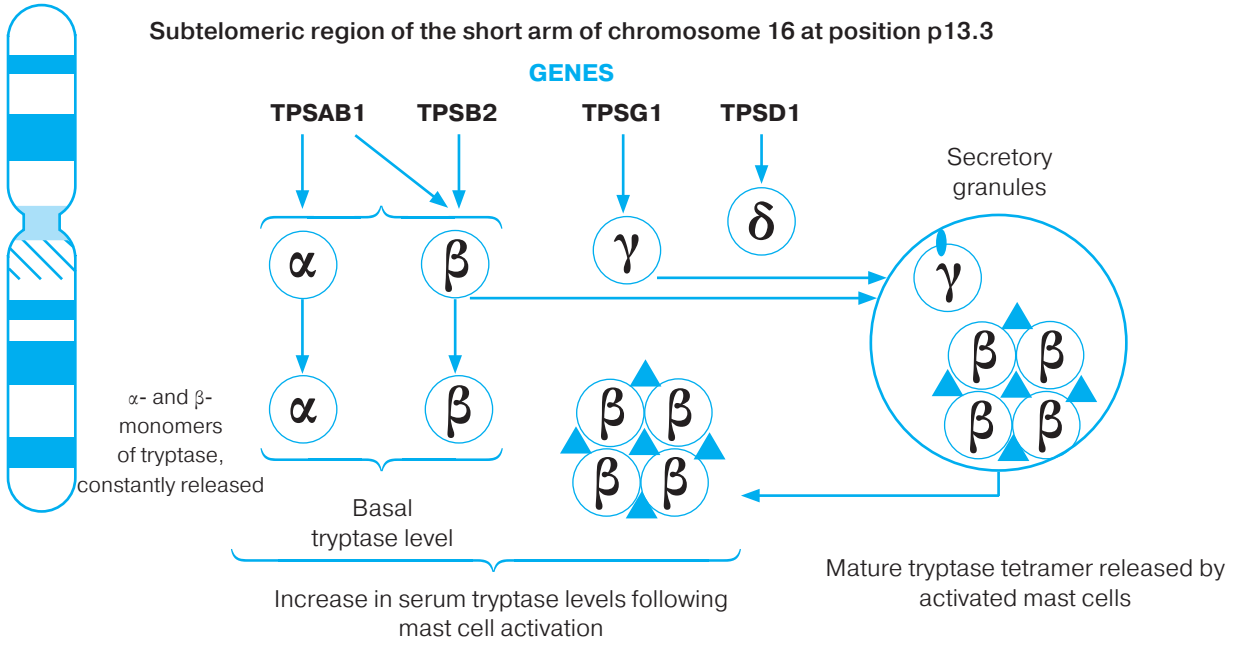

Fig. 1. **Production and intracellular transport of human α-, β-, and γ-tryptases in mast cells (illustration by the author)**
Рис. 1. **Производство и внутриклеточный перенос человеческих α-, β- и γ-триптаз в тучных клетках (иллюстрация автора)**

HUMAN TRYPTASE GENETICS

The human tryptase locus is located in the subtelomeric region of the short arm of chromosome 16 at position p13.3. All four known genes encoding tryptase (TPSG1, TPSB2, TPSAB1, and TPSD1) are located in this locus [9, 10]. As it is typical for subtelomeric regions, the tryptase locus contains large segments of homologous repetitive sequences that facilitate gene conversion and replication. Human tryptases are believed to have evolved in this region through tandem duplication, which may help explain the high degree of homology between human tryptase isoforms. The two most studied loci are TPSB2 and TPSAB1, which encode biologically important secreted tryptase isoforms consisting of α- and β-tryptase. While TPSAB1 can encode either α or β-tryptase, TPSB2 encodes only β-tryptase (βI, βII, or βIII-tryptase) [2].

Elevated basal serum tryptase levels, consisting of secreted zimogen α-protryptase and β-protryptase, consisting of secreted zimogen α-protryptase and β-protryptase, are inherited in an autosomal dominant manner in humans. This increase in basal serum tryptase levels is the result of TPSAB1 duplications, which encode α-tryptase, a genetic trait known as hereditary α-tryptasemia. However, the increase in basal serum tryptase levels far exceeds what would be expected based solely on the excess number of copies. It has been suggested that the increase in basal serum tryptase levels is mainly the result of overexpression of tryptase on the replication-competent allele, but this has not been proven. Indeed, individuals carrying up to four additional copies of TPSAB1 have been reported to date, and it has been shown that basal serum tryptase levels follow a dose-response effect, with each additional replication of TPSAB1 increasing basal serum tryptase levels by approximately 9.5 ng/ml [11, 12].

There have also been reports of copy number loss in the tryptase locus, but it is unclear whether these structural variants exist in the TPSAB1 or TPSB2 locus. An increase in the number of copies encoding β-tryptase has also been reported, but where it is present, it has not been shown to correlate with elevated basal serum tryptase levels, and it is currently unknown whether these replicates exist in TPSAB1 or TPSB2. Ultimately, the location of these duplications or deletions may be arbitrary, given that any locus can encode any of the known active versions of β-tryptase (βI- III) [13].

The tryptase gene undergoes various mutations, leading to insufficient transcription, zymogen activation, catalytic site conformation, and even gene deletion as a whole [14]. Tryptase gene polymorphisms are numerous, and the number of functional

tryptase alleles that a person can carry varies from two to four [15]. The number and type of functional alleles carried by an individual can alter baseline systemic tryptase levels. Genetics affects baseline serum tryptase levels [16, 17].

TRYPTASE SECRETION

Tryptase is produced in the form of α-, β-, γ-, and δ-subunits in the endoplasmic reticulum. While the γ subunit remains bound to the membrane of secretory granules, α and β monomers are continuously released as enzymatically inactive propeptides into the bloodstream without a specific stimulus and constitute the tryptase normally present in serum [18]. In addition, the α- and β-subunits undergo sequential proteolytic cleavage (activation). Initially, various forms of tryptase are expressed as pre-tryptases, then they rapidly convert to pro-tryptases to become mature (mainly β) tetrameric tryptase, which is active, stabilized by heparin, and stored in secretory granules, awaiting appropriate stimuli to induce degranulation. Cathepsins B, L, or C are also required for conversion to mature tryptase. In addition, β-tryptase remains stable after proteolysis with the help of heparin. Heparanase deficiency leads to an increase in tryptase stores in mast cells due to the formation of larger heparin chains [4, 18]. Conversely, defects in heparin synthesis contribute to a decrease in the accumulation of the active form of tryptase [4].

Genetic factors (number and type of functional alleles) or activation of mast cells for other reasons also affect tryptase content. Thus, mast cell activation and tryptase levels are determined by genetic, exogenous, and cellular factors [19].

Mature heterotetrameric β-tryptase has high biological activity against tissues, cells, and molecules and consists of four non-covalently bound subunits, each monomer containing an active enzyme site. α-tryptase also forms mature homotetrameric complexes, but in smaller quantities. Both tetrameric α- and β-tryptase are released by activated (degranulating) mast cells, and a temporary increase in serum tryptase levels reflects this process. For example, in IgE-dependent allergic reactions, an increase in serum tryptase concentration can be measured as early as 15 minutes after activation, with a peak in 2 hours [3, 20].

When mast cells are activated, the release of contents into the extracellular space occurs within minutes. Regardless of the cause, as a result of mast cell degranulation, a rapid increase in histamine levels in peripheral blood is observed within 5 minutes after the onset of the first symptoms, while the detection of tryptase is delayed by 15 or 20 minutes due to the bulky heparin shell. This difference cannot be overlooked in human medicine because it explains why histamine and tryptase cannot be optimally measured in the same blood sample. Indeed, while histamine can peak 5–10 minutes after the onset of anaphylaxis symptoms, tryptase measurements at such early time points often yield values below 12 μg/L, which are mistakenly considered “normal” or even “negative” [21, 22].

Baseline serum tryptase levels are the result of continuous release of immature α- and β-tryptase monomers; mature tetrameric β-tryptase is stored in specialized secretory granules, where it is stabilized by the interaction of proteoglycans with heparin [19, 22]. Mature β-tryptase is not released continuously, but as a result of mast cell activation. Thus, serum tryptase levels measured after mast cell degranulation include both immature and mature forms of α- and β-tryptase. γ-tryptase is a membrane-bound monomer [23].

From a functional point of view, mature tryptase performs sequential actions (Fig. 2) After degranula-

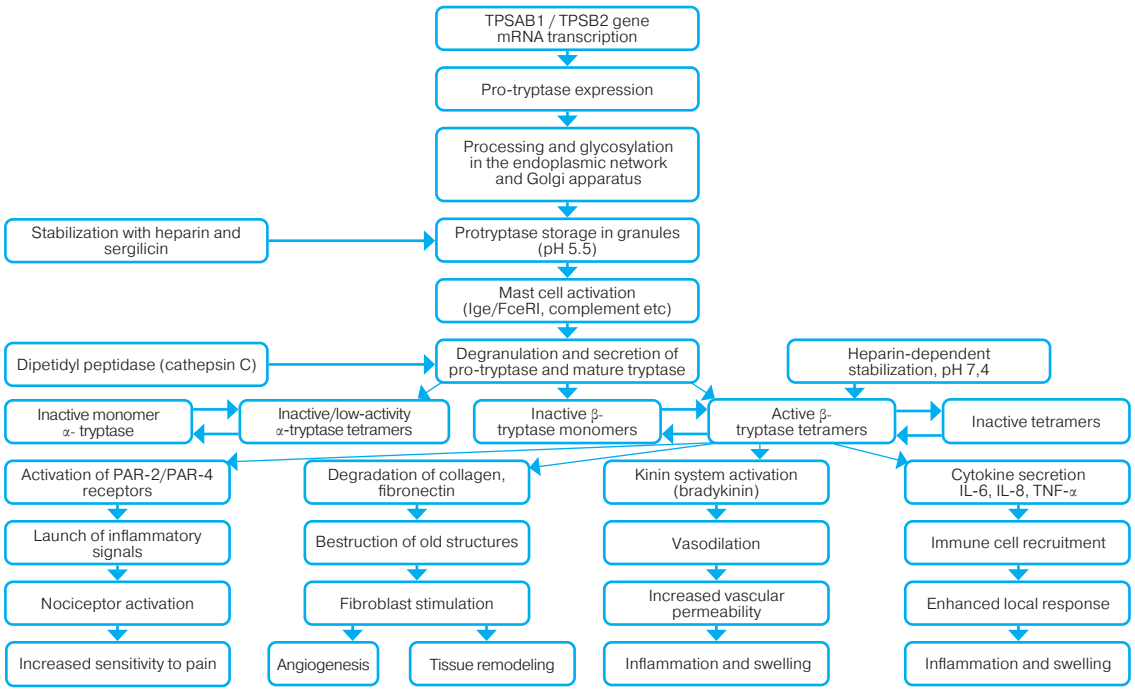

Fig. 2. **The biochemical mechanism of action of tryptase (illustration by the author)**
Рис. 2. **Биохимический механизм действия триптазы (иллюстрация автора)**

tion of mast cells, mature tryptase acts as a vasoactive agent in the early stages, increasing vascular permeability and promoting edema, as a pro-inflammatory mediator activating various types of immune cells, including neutrophils and eosinophils, as a chemotactic factor attracting leukocytes and enhancing the inflammatory response, and as a priming agent increasing tissue sensitivity to affect other inflammatory mediators, including histamine and prostaglandins [24, 25]. Under the action of degranulated tryptase, the formation of bradykinins from kinins contributes to increased vascular permeability, while the extracellular matrix is destroyed, which promotes cell migration. Tryptase induces the recruitment and activation of leukocytes with a specific chemotactic effect on neutrophils and eosinophils, which participate in the late phase of allergic inflammation. Tryptase promotes interaction between mast cells and the mononuclear phagocytic system. In the late stages of the inflammatory process, tryptase activates a regenerative function, promoting tissue repair [26]. It stimulates the proliferation and activation of fibroblasts, which promotes the synthesis of extracellular matrix components such as collagen and fibronectin. Tryptase also promotes angiogenesis to activate endothelial cells and induce the formation of new capillaries. These processes are an important part of tissue remodeling and ensure the restoration of tissue structure and function after inflammatory damage. More recent data indicate the role of tryptase in the onset of pain, such as postoperative pain due to the activation of nociceptive receptors activated by protease [27, 28].

Research has traditionally focused almost exclusively on tryptase as an extracellular mediator, but the latest data indicate the role of tryptase in the homeostasis of nuclear histones in mast cells and in the disorganization of histone frameworks during cell death [29].

Human tryptase is considered to be almost specific to mast cells, which can contain large amounts, up to 35 pg per cell. Basophils also contain and release

tryptase, but they do not contribute significantly to tryptase levels, according to reports that showed their tryptase content was 100 times lower than that of mast cells [30]. Tryptase load varies greatly both in mast cells, depending on their microenvironment, and in basophils, ranging from 1 to 100 in different human donors. Human basophils are capable of secreting tryptase upon IgE-mediated activation [31]. In accordance with tryptase synthesis and exocytosis, as described above, it is important to bear in mind that the level of circulating tryptase measured at any given time in a given individual is the combined result of the activation of the total number of mast cells ("mast cell load"), their genetically determined level of α- and β-tryptase production, and their status leading to the release of mature tryptase.

CONCLUSION

The collected data on the secretion and functions of tryptase produced by mast cells allow us to consider it a multifunctional mediator that acts through specific molecular and cellular mechanisms. Tryptase attracts particular attention due to its involvement in the pathogenesis of inflammatory processes and allergic reactions in various organs and systems, including the respiratory system and skin. In addition, tryptase plays a key role in the regulation of tissue remodeling and healing processes, ensuring homeostasis and tissue repair after damage. Studying the biological effects of tryptase helps deepen our understanding of the functional capabilities of mast cells, opening up new avenues for the diagnosis and treatment of diseases of high social significance.

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FINANCING SOURCE

The authors declare that no funding was received for this study.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

AUTHORS CONTRIBUTIONS TO THE WORK

Natalia E. Tarasova — conceptualization, methodology, data curation, writing — review & editing — preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision — including pre- or post-publication stages.

Alexander A. Lebedenko — supervision, project administration.

Olga E. Semernik — conceptualization, validation, project administration.

Natalya V. Dobaeva — supervision, project administration.

Viktoriya O. Skosar — investigation, writing.

Nina U. Haygetyan — visualization.

Ilya P. Krivokhlyabov — data curation.

Stepan P. Shkilnyuk — visualization.

ВКЛАД АВТОРОВ В РАБОТУ

Тарасова Н. Е. — разработка концепции, проведение исследования, подготовка текста — оценка и редактирование — подготовка, создание и презентация опубликованной работы.

Лебеденко А. А. — консультации, управление проектом.

Семерник О. Е. — разработка концепции, проверка, управление проектом.

Добаева Н. М. — консультации, управление проектом.

Скосарь В. О. — подготовка текста.

Хейгетян Н. Ю. — визуализация.

Кривохлябов И. П. — подготовка, работа с данными.

Шкильнюк С. П. — визуализация.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association “Ethical Principles of Conducting Scientific Medical Research with human Participation” as amended in 2000 and the “Rules of Clinical Practice in the Russian Federation” approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the Interdisciplinary Local Ethics Committee of the Pacific State Medical University of the Ministry of Health of the Russian Federation.

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

Исследование было проведено с учетом требований Хельсинкской декларации Всемирной ассоциации «Этические принципы проведения научных медицинских исследований с участием человека» с поправками 2000 г. и «Правил клинической практики в Российской Федерации», утвержденных Приказом Министерства здравоохранения РФ от 19.06.2003, № 266. Данное исследование было одобрено Междисциплинарным локальным комитетом по этике ФГБОУ ВО ТГМУ Министерства здравоохранения РФ.

Обзор / Review

Allergic rhinitis in children with obesity: a modern view of the problem

REV — обзорная статья

https://doi.org/10.53529/2500-1175-2025-2-15-28

Date of receipt: 29.12.2024
Date of acceptance: 10.05.2025
Date of publication: 17.06.2025

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Abstract

Relevance. In recent decades, there has been an increase in a number of non-communicable chronic diseases and treated as a global health priority. There is an increase in the prevalence of allergic diseases, including allergic rhinitis (AR), and obesity in the pediatric population. In this regard, the study of AR in children with comorbid obesity is of particular interest.

The aim of the review is to summarize current data on the immunological and clinical-epidemiological features of AR in children with comorbid obesity.

Content. The review presents current information on the role of individual cytokines and adipokines in the development of chronic systemic inflammation in children with AR and obesity. An analysis of literature data on the significance of obesity as a possible risk factor for the development of AR in childhood is conducted. Clinical and epidemiological features are discussed, and individual studies are presented on some aspects of AR therapy in obese patients.

Conclusions. The analysis showed that the currently available data on the relationship between AR and overweight/obesity in children are contradictory and require further research.

Keywords: allergic rhinitis, obesity, cytokines, interleukin-33, interleukin-1β, leptin, adiponectin

Conflict of interest:
Meshkova R.Y. is a member of the editorial board of the journal, but did not influence the decision to publish this article. The article has passed the review procedure review procedure adopted in the journal. The authors do not report any other conflicts of interest declared

For citation: Koroleva A.E., Bekezin V.V., Meshkova R.Y. Allergic rhinitis in children with obesity: a modern view of the problem. *Allergology and Immunology in Pediatrics*. 2025; 23 (2): 15–28. https://doi.org/10.53529/2500-1175-2025-2-15-28

Аллергический ринит у детей с ожирением: современный взгляд на проблему

https://doi.org/10.53529/2500-1175-2025-2-15-28

УДК 616.211-002.193-056.3:616-056.52
Дата поступления: 29.12.2024
Дата принятия: 10.05.2025
Дата публикации: 17.06.2025

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Резюме

Актуальность. В последние десятилетия отмечается эпидемический рост ряда неинфекционных хронических заболеваний, являющихся глобальной проблемой здравоохранения. В детской популяции наблюдается увеличение распространенности как аллергического ринита (АР), так и ожирения. В связи с этим представляет особый интерес изучение АР у детей с коморбидным ожирением.

Целью обзора является обобщение современных данных об иммунологических и клинико-эпидемиологических особенностях АР у детей с коморбидным ожирением.

Содержание. В обзоре представлены актуальные сведения о роли отдельных цитокинов и адипокинов в формировании хронического системного воспаления у детей с АР на фоне избытка жировой массы тела. Проведен анализ литературных данных о значении ожирения как возможного фактора риска развития АР в детском возрасте. Обсуждены клинико-эпидемиологические особенности, а также приведены единичные исследования, касающиеся некоторых аспектов терапии АР у пациентов с ожирением.

Заключение. Проведенный анализ показал, что имеющиеся на сегодняшний день данные о наличии связи АР и избытка массы тела / ожирения у детей носят противоречивый характер и требуют проведения дальнейших исследований.

Ключевые слова: аллергический ринит, ожирение, цитокины, интерлейкин-33, интерлейкин-1β, лептин, адипонектин

Конфликт интересов:
Мешкова Р. Я. — член редакционной коллегии журнала, но не влияла на решение опубликовать эту статью. Статья прошла принятую в журнале процедуру рецензирования. Об иных конфликтах интересов авторы не заявляли.

Для цитирования: Королева А. Е., Бекезин В. В., Мешкова Р. Я. Аллергический ринит у детей с ожирением: современный взгляд на проблему. *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 15–28. https://doi.org/10.53529/2500-1175-2025-2-15-28

INTRODUCTION

In recent decades, the epidemic growth of allergic diseases has become a serious problem for global health [1]. AR is one of the most common chronic diseases in the world and is associated with a significant deterioration in the quality of life of patients [2]. Risk factors for AR include genetic predisposition, high socioeconomic status, maternal smoking during the first year of a child's life, and a history of cesarean section [2]. At the same time, recent studies show that excess body fat in children can be considered one of the predictors of AR development [3]. It is assumed that the link between excess body weight/obesity and AR is due to common pathophysiological mechanisms [3, 4]. Obesity is characterized by hypertrophy of white adipose tissue and impaired metabolic activity of adipocytes, leading to chronic systemic inflammation [4, 5]. In turn, changes in the levels of adipokines secreted by adipose tissue can cause a shift in the immune response toward the Th2 type, which increases the risk of allergic diseases [4, 6, 7].

It should be noted that modern literature provides contradictory data regarding the link between obesity and AR [3, 8]. Thus, it is important to summarize current data on the possible effect of obesity on the development of AR and the characteristics of the disease, as well as on the mechanisms underlying these processes.

PATHOGENETIC FEATURES OF ALLERGIC RHINITIS IN CHILDREN WITH OBESITY

It is assumed that there is some commonality between obesity and AR in terms of pathophysiological mechanisms, in particular, changes in the production of pro- and anti-inflammatory cytokines and adipokines [9, 10]. However, the exact mechanism explaining the possible link between obesity and AR remains unclear [7,10].

Leptin is one of the hormones produced by adipose tissue that regulates energy metabolism. Leptin promotes the production of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), and stimulates the proliferation of Th1 cells [10]. Recent data indicate that patients with RA and comorbid obesity have elevated serum leptin levels, which correlate with the severity of RA [11–15, 23].

According to Wang X. et al., children with AR and obesity had a significant increase in leptin and ILC2 (type 2 innate lymphoid cells) levels in the blood compared to children with AR and normal body weight, as well as the control group (healthy children). It has been shown that the administration of recombinant leptin to children with AR and obesity led to an increase in ILC2 levels in the blood [11]. It is worth noting that similar results were obtained in another study in adult patients with AR who were

obese [12]. According to the authors, the leptin/ILC2 axis in obese patients may exacerbate chronic systemic inflammation and contribute to the development of severe AR [11, 12]. It is assumed that leptin enhances the activation of inflammatory cells in AR against the background of obesity. In a study by Liu W. et al., elevated serum leptin levels in children with AR were positively correlated with levels of eosinophils, eosinophil cationic protein (ECP), C-reactive protein (CRP), interleukin-5 (IL-5), and interleukin-17 (IL-17) [13].

The possible role of osteopontin protein in allergy and obesity is discussed. Osteopontin is a pro-inflammatory cytokine secreted by osteoblasts, fibroblasts, epithelial cells, activated macrophages and T-lymphocytes [16]. A number of studies have shown that in children with AR and obesity there is a significant increase in the level of leptin and osteopontin in the serum of rabbits compared to the control group, as well as a positive correlation with the severity of AR. The level of osteopontin was found to correlate with the level of eosinophils and ECB in serum. Thus, increased expression of leptin and osteopontin may play an important role in the pathogenesis of chronic inflammation in AR and morbid obesity, contributing to the enhancement of Th2 response, as well as regulating apoptosis, adhesion, migration and activation of eosinophils [16, 17].

It should be noted that there are studies in the literature that did not reveal statistically significant differences between leptin levels and the severity/character of AR course in obese patients [18, 19]. Thus, a cross-sectional study showed that in 7-10 years old overweight/obese children (according to bioimpedance-sometry data) no significant differences in serum leptin levels were found depending on the nature of AR course (persistent/intermittent) [18]. In a study by Kalpa- klioglu A.F. et al. there was no association between serum leptin levels and the severity of AR, as well as sensitization to allergens in adult patients [19].

Altered adiponectin secretion possibly contributes to the development of chronic systemic inflammation in patients with AR and comorbid obesity. However, there are very few studies devoted to this problem [4, 7]. It is known that in obesity there is a decrease in the level of adiponectin, an adipose tissue hormone with an anti-inflammatory effect [5, 7]. n an experimental study on a mouse model, it was shown that exogenous administration of adiponectin attenuated the development of ovalbumin-induced airway hyperreactivity by reducing the number of eosinophils and decreasing the level of Th2-type cytokines [22]. In a cross-sectional study, it was found that children 4-10 years old with first-diagnosed AR had lower serum adiponectin levels compared to healthy controls and positively correlated with the severity of AR. Adiponectin levels were negatively correlated with serum ECB levels, while there was no correlation with interleukin-1β (IL-1β), IL-6, TNF-α, IL-10 and total IgE levels [14]. In another study, serum adiponectin levels in children 7-10 years old with AR and obesity had no significant differences compared to the control group. Comparative analysis of adiponectin levels in children with AR and obesity did not reveal statistically significant differences depending on the nature of AR course [18].

Interleukin-1β (IL-1β) is considered as another mediator of allergic inflammation. In AR, IL-1β levels may be associated with inflammation caused by exposure to allergens, as well as with the main clinical symptoms of the disease - nasal itching and rhinorrhea [21]. It should be noted that there are single clinical studies in the literature devoted to the study of the role of IL-1β in AR on the background of excess adipose tissue. According to a number of authors, IL-1β can be a potential biomarker and predictor of severe persistent AR [22, 23, 24]. According to Han M.W. et al. data, IL-1β level positively correlates with AR severity and is also a significant risk factor for the development of moderate and severe persistent AR (4.7-fold increase in risk) [22]. According

to another study, children with AR and obesity have higher IL-1β levels compared to children with AR and normal body weight. It is shown that elevated IL- 1β level (5.8-fold increase in risk) and elevated leptin level (11.3-fold increase in risk) are significant risk factors for moderate to severe persistent AR. The authors found that the majority of children with AR have increased serum IL-1β and leptin levels during weight gain. In turn, in some children with obesity and AR, a decrease in blood levels of IL-1β and leptin was observed during weight correction [23]. In another study, the authors showed that in the group of obese children IL-1β level depends on the nature of AR course, namely IL-1β level in children with persistent AR was significantly higher compared to children with intermittent AR course [24].

Interleukin-33 (IL-33) is a cytokine "alarmin" (alarm signal) that can accumulate and be rapidly released into the extracellular space during cell/tissue damage, affecting immune cells expressing ST2 receptor on their surface [25, 26]. IL- 33 is synthesized mainly by epithelial cells, fibroblasts, endothelial cells, and adipose tissue cells - adipocytes. It is known that IL-33 is produced by the cells of the first line of defense, in particular epithelial cells, when they are exposed to allergens [27, 28]. In vitro studies have shown that IL-33/ ST2 causes activation of ILC2, which induce Th2 response and tissue remodeling by producing Th2-type cytokines [29, 30]. In adipose tissue, IL-33 is involved in the interaction between adipocytes and immune cells [31]. Exposure of IL-33 to ILC2 cells leads to their activation and secretion of IL-5, IL-13. In turn, IL-13 directly affects pre-adipocytes and promotes their maturation [32]. IL-33 interacts with Treg having ST2-receptor on its surface, which causes synthesis of IL-10 by these cells, which causes alternative activation of macrophages and their synthesis of catecholamines aimed at maturation of pre-adipocytes into adipocytes [32, 33]. According to Glück J. et al., adult patients with intermittent seasonal AR have elevated serum IL-33 levels that correlate with the severity of AR [32]. In a cross-sectional study, it was shown for the first time that children 7-10 years old with overweight/obesity and AR showed increased serum IL-33 levels compared to the control group. In children with excess body fat mass the IL-33 level depended on the nature of AR course, in particular, in children with persistent AR the IL-33 content was significantly lower compared to children with intermittent AR. An inverse correlation between IL-33 level and %FMT was found to be lower in intermittent AR compared to children with intermittent AR [24].

Thus, few data from the literature suggest a possible role of cytokines IL1β, IL-33, osteopontin and adipokines (leptin, adiponectin) in AR and comorbid obesity in children. However, further prospective studies are needed to clarify the potential mechanisms of the association between AR and pediatric obesity.

IS OBESITY A RISK FACTOR FOR ALLERGIC RHINITIS: WHAT IS KNOWN?

Currently, there is no consensus on the role of overweight/obesity as a risk factor for the development of AR (Table 1). A large number of studies indicate an association between high BMI and the risk of AR development in children [34-37]. It is important to note that the cross-sectional and retrospective design of these studies does not allow assessing whether increased BMI preceded the development of AR in children.

There are few examples of prospective studies on this topic in the current literature. For example, Vehapoglu A. et al. found that prepubertal obese children have a higher risk of developing AR and BA compared to children with normal body weight [38]. In another study, an increase in BMI in children aged 16-18 years was associated with an increased risk of developing AR, but not BA and AD [39].

Few studies are available to assess the dynamics of body weight after birth and its possible impact on the future development of AR in children. In a retrospective study, excessive weight gain after birth was found to be associated with the risk of developing AR and atopic dermatitis (AD) in adolescence, especially in children born with low birth weight [40].

However, Mai X.M. et al. reported that no association between large birth weight (⩾90th percentile) and the presence of AR and AD symptoms was found in 4-year-old children [41]. Chang C.L. et al. studied the association between BMI after birth and the risk of allergic diseases (AR, food allergy) in children aged 6, 12, and 18 years.The risk factors for AR in children were found to be delayed fetal intrauterine development, insufficient weight gain, maternal heredity for allergy, but not excessive weight gain during the first two years of life [42].

In a meta-analysis of 30 studies, high BMI was associated with an increased risk of AR in children but not in adults [3]. In another systematic review and metaanalysis of 32 studies, high or low BMI was not associated with the risk of developing AR in both children and adults [8]. However, in this paper [8], unlike the previous meta-analysis [3], data in children were evaluated in age-dependent subgroups: under 12 years of age and between 13-18 years of age. It is worth noting that both meta-analyses included studies based on self-reports of AR symptoms and self-reported anthropometric measurements, which could influence the authors' conclusions in a different way [3, 8].

There are also data in the literature in which excess body fat mass in children was not a risk factor for AR [43-47]. According to the results of phase II studies, ISAAC ("International study of asthma and allergies in childhood") involving 10,652 children 8-12 years of age found no association between high BMI and AR [43]. In several cross-sectional studies in children, high BMI had a negative association with AR [44, 45]. A study by Scaaby T. et al. using Mendelian randomization found an association between overweight/obesity and higher prevalence of AD, decreased lung function in patients older than 16 years, but not with AR [46]. According to the data presented by Han Y.Y. et al. in children, central obesity is associated with a reduced risk of AR [47].

The ambiguity of the study results is probably related to the design features, as well as to the different methods of AR verification and overweight/obesity in children. It is worth noting that the literature on this problem is dominated by studies with a cross-sectional or retrospective design, which do not allow to determine the presence of causality [33-37, 40, 43, 44, 46, 47]. In some studies, the criterion for children inclusion was the presence of a physician-verified diagnosis of AR [33, 37, 38, 41, 42], whereas in other studies the assessment of AR symptoms was based only on parent/child questionnaire data [36, 39, 40, 44, 47]. A number of studies analyzed self-reports of patients and/or parents of children, which served to further identify groups of children for additional allergologic examination and confirmation of AR diagnosis [34, 35, 43, 46]. The children's anthropometric indicators at the time of their inclusion in the study were assessed both by medical personnel [33- 35, 37, 38, 41, 43, 44, 47] and parents [39, 36, 40, 42, 46]. All this causes certain difficulties when analyzing scientific works on this topic.

Thus, there are few and rather contradictory studies investigating the possible role of overweight/obesity as a risk factor for AR in children. It is still unclear which values of increased BMI are associated with the development of AR, since both overweight and obese children were included in the studies. It should be noted that in most studies the presence of excess body fat mass in children was diagnosed using the BMI criterion [33-46], which does not allow determining the actual distribution of body fat [48, 49]. According to a meta-analysis, BMI is characterized by low sensitivity and does not identify more than a quarter of overweight/obese children [49]. This raises the question of whether further studies investigating AR in children with excess body fat mass should use the generally accepted BMI or use other more accurate methods of assessing body composition. In addition, the propensity of obese children to develop AR is likely to be influenced by interactions with other factors such as sex, race, aggravated heredity and the presence of comorbid allergic diseases, which should be considered in future studies.

PECULIARITIES OF CLINICAL SYMPTOMATOLOGY AND PREVALENCE OF ALLERGIC RHINITIS IN CHILDREN WITH OBESITY

It is of interest to study the clinical features of AR in children with excess body fat mass. Thus, in

Table 1. **Results of clinical studies in children with allergic rhinitis and obesity (authors' table)**
Таблица 1. **Результаты клинических исследований у детей с аллергическим ринитом и коморбидным ожирением (таблица автора)**

Author, year	Country	Type of study	Sample size	Age of children	Main outcome
Lei Y., et al., 2016 [33]	China	Cross-sectional study	3327 children	3 age groups: 2–6, 7–12, 13–14	Obesity in children is a risk factor of AR and AD, but not BA, FA and DA
Saadeh D. et al., 2014 [34]	France	Cross-sectional study	6733 children	9–11	High BMI is a risk factor for AR and BA
Baumann L.M. et al., 2015 [35]	Pery	Cross-sectional study	1441 children	13–15	High BMI is a risk factor for AR
Lim M.S. et al., 2017 [36]	South Korea	Cross-sectional study	53 769 children	12–18	High BMI is associated with AR and AD
Vehapoglu A., et al., 2021 [38]	Turkey	Prospective study	707 children	3–10	Overweight/obesity is associated with a high risk of AR and BA
Kreißl S. et al., 2014 [39]	Germany	Prospective study	3000 children	Evaluation at the age of 9–11 and 16–18	Increase in BMI is associated with a high risk of AR, but not BA and AD
Lin M.H. et al., 2015 [40]	Taiwan	Retrospective study	74 688 children	13–15	Excessive body weight gain. after birth may be a risk factor for AR and AD development
Mai X.M., et al., 2007 [41]	Sweden	Prospective study	4089 children	Evaluation at the age of 1, 2 and 4	Birth weight ⩾ 90th percentile and high BMI in early childhood are not a risk for AR at the age of 4
Chang C.L., et al., 2022 [42]	Australia	Prospective study	620 children	Evaluative at the age of 6, 12 and 18	Excess body weight is not associated with a risk of AR at the age of 18
T. Kusunoki et al., 2007 [44]	Japan	Cross-sectional study	50 086 children	7–15	The inverse association is between childhood obesity and prevalence of AR and AC. Obesity in children is associated with prevalence of BA and severity of AD
Leung T.F., et al., 2009 [45]	China	Cross-sectional study	486 children	14–16	Obesity is not associated with AR and BA
Y.Y. Han et al., 2007 [47]	USA	Cross-sectional study	2358 children	6–17	Central obesity is associated with a decreased risk of AR, particularly among boys

Note: FA — food allergy, DA — drug allergy, AC — allergic conjunctivitis.

some studies, the authors demonstrated the presence of an association between obesity and the severity of AR [13, 18, 24, 39]. According to a prospective study of 1794 children observed from 9-11 years to 16-18 years, an increase in BMI was a risk factor for persistent AR [50]. In the work of Han M.W. it was shown that in some children with mild AR and normal body weight on the background of weight gain there was observed aggravation of nasal symptoms and development of severe AR [23]. At the same time, in the work of Kusunoki T. et al. no association was found between obesity and severity of AR in children. In this paper, the presence of AR was assessed by parental questionnaires and patients with other allergic diseases (AD, AD, AU) were included in the study [44].

It should be noted that in the vast majority of studies, the authors used BMI to assess obesity, which does not distinguish between fat and muscle mass in the body, nor does it take into account the distribution of fat deposits [49, 50]. In a few studies, the presence of obesity was assessed by bioimpedanceometry [13, 18]. In particular, by the % body fat

mass (%BFM), which reflects the presence and degree of fat deposition in the body [51, 52]. Thus, Liu W. et al. found that in 3126 children aged 7-12 years, obesity (according to %BFM, waist circumference, and BMI) was a risk for severe year-round AR [13]. According to a cross-sectional study, 7-10 years old overweight/obese children (according to %BFM) had an earlier manifestation of AR (up to 3 years of age) with nasal pruritus predominating as the main manifestation of rhinitis. Excess body fat mass was a predictor of persistent AR course in primary school children [18].

Children with AR and comorbid obesity may be more susceptible to air pollution. The results of Li R. L. et al. indicate that carbon monoxide (CO) and ambient particles less than 10 μm in diameter (PM10) and PM2.5 lead to worsening nasal symptoms of AR in obese children compared to the ones of control group [53].

It is of interest to study the possible role of excess body fat mass in the formation of a certain type of sensitization. According to a study, children 4-8 years old with AR and increased BMI were 2.64 times more likely to be monosensitized to aeroallergens of house dust mites compared to children with AR and normal BMI [54]. It has also been shown that skin reactivity to histamine in adult patients with AR may depend on body fat mass. According to a study by Park D. Y. et al. observed a positive correlation between high BMI and skin reactivity to histamine in patients with AR [55]. In experimental studies it was shown that histamine level can be increased as a result of the release of substance P, which leads to neurogenic inflammation [56, 57]. Thus, according to the authors, the increased content of substance P may be a mediator of allergy, providing higher skin reactivity to histamine in obesity [55, 56, 57].

A number of epidemiologic studies have established higher prevalence rates of AR among overweight/obese children compared to children with normal body weight [33, 35, 37]. At the same time, Liu W. et al. found that the prevalence of obesity in the group of children with AR was comparable to children in the control group [13].

In addition, children with AR have a pronounced decrease in quality of life parameters related to physical activity. According to Park J. H. et al., children with AR symptoms (rhinorrhea, nasal congestion, sneezing, nasal itching, sleep disturbance) are more prone to sedentary lifestyle than AD patients and control group children. At the same time, higher BMI values were observed in the group of children with AR at the time of the study compared to children in the control group. According to the authors, children with AR have a higher probability of obesity. It should be noted that in the study, the level of physical activity was assessed based on children's self-reported physical activity rather than objective measurements (e.g., accelerometer), which may have led to underestimation or overestimation of the relationship between the level of physical activity, BMI and AR [58].

Given that most studies have a cross-sectional design, it remains unclear whether excess body fat mass/obesity in children precedes the development of the identified clinical features of AR. On the other hand, it is possible that patients with certain features of AR are more likely to gain weight. To answer these questions, further prospective studies using strict diagnostic criteria for AR and the use of methods to assess the presence and degree of body fat deposition are needed. In addition, epidemiologic studies are needed to assess the prevalence of AR in children of different ages with comorbid obesity.

TREATMENT OF PATIENTS WITH ALLERGIC RHINITIS AND OBESITY

Despite the fact that the principles of therapy have not been developed for individuals with AR and obesity, single studies have demonstrated var-

ious aspects of treatment in these patients [23, 59]. According to the data of Han M.W. et al., improvement of nasal symptoms from severe to mild AR was observed in a part of children on the background of BMI reduction [23]. At present, it is difficult to say whether body fat mass affects the response of patients with AR to treatment with intranasal glucocorticosteroids (INGCS). In a recent prospective study of the efficacy of INGCS in adult patients with AR and elevated BMI, it was shown that symptom improvement was observed after a 30-day course of treatment in both obese and normal weight patient groups. AR symptoms were assessed using the Visual analogue scale (VAS), SNOT- 22 (Sino-Nasal Outcome Test-22) and NOSE-5 (Nasal obstruction symptom evaluation-5) questionnaires, as well as an increase in peak nasal inspiratory flow (PNIF). At the same time, the authors showed that patients with AR and obesity had a statistically significant decrease in IL-10 levels in the nasal mucosa after therapy compared to the group with AR and normal body weight. Thus, according to the authors' opinion, individuals with AR and obesity have a weaker anti-inflammatory response to INGCS therapy [59].

Thus, no studies on the efficacy of INGCS in children with AR and obesity were found in the literature available to us. This leads to another unanswered question: whether weight loss in obese children can improve the results of AR treatment with the use of INGCS. In general, there is insufficient work on the role of weight loss as an additional factor in influencing symptoms and efficacy of AR treatment in children. Further study of the impact of obesity on the treatment of children with AR, as well as weight correction is important from the point of view of personalized tactics of managing such patients.

CONCLUSION

Obesity is characterized by chronic sluggish inflammation, which can influence the immune system and possibly contribute to the pathogenesis of AR. To date, there is no consensus on which of the potential mechanisms mediates the association between AR and obesity. Summarizing these studies, we can conclude that patients with AR and excess body fat mass have an imbalance of IL-33, IL-1β, osteopontin, and a number of adipokines (leptin, adiponectin). Given the limited data, it is currently difficult to say which of these are most clinically important.

At present, the question of whether overweight/obesity is a risk factor for AR in children remains incompletely resolved. There is evidence that obesity may affect the severity of AR. At the same time, there are a number of studies in the literature that have not found an association between these diseases.

In general, studies on the causal relationship between obesity and AR are few and contradictory. In our opinion, it is of particular interest to continue studying the role of cytokines and adipokines in AR on the background of excess body fat mass. In addition, it remains unclear whether excess body fat mass/obesity in children precedes the development of the identified clinical features of AR, or whether patients with certain clinical features are more likely to gain weight. Future work should include studies related to weight management to assess the clinical and pathophysiologic significance of the putative mechanisms underlying the association between AR and excess body fat mass. It is of interest to study the impact of obesity on the therapy of children with AR, as well as to evaluate whether weight management can improve the response to INGCS treatment in children with AR. All this calls for further in-depth study of AR in overweight/obese children.

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FINANCING SOURCE

The authors declare that no funding was received for this study.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

THE AUTHORS' CONTRIBUTION TO THE WORK

Anna E. Koroleva — conceptualization, writing — review & editing — preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision — including pre- or post-publication stages.

Vladimir V. Bekezin — conceptualization.

Raisa Y. Meshkova — conceptualization, writing — review & editing — preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review.

ВКЛАД АВТОРОВ В РАБОТУ

Королева А. Е. — разработка концепции, подготовка текста — оценка и редактирование — подготовка, создание и презентация опубликованной работы.

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Мешкова Р. Я. — разработка концепции, подготовка текста — оценка и редактирование.

Обзор / Review

Principles of treatment of contact allergic dermatitis: features associated with children and adolescents

REV — обзорная статья

https://doi.org/10.53529/2500-1175-2025-2-29-37

Date of receipt: 09.01.2024
Date of acceptance: 23.05.2025
Date of publication: 17.06.2025

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Abstract

Introduction. Contact allergic dermatitis (CAD) is known to be one of the most prevalent allergic diseases of skin, so its research is of a high interest. Besides clarification of modern approaches to the treatment of contact allergic dermatitis is undoubtedly of current interest. The increase in the growth of contact allergic dermatitis in children explains the relevance of solving the problem of treating the disease in this age group.

Purpose of the lecture. The purpose of this lecture is to review modern approaches to the treatment of contact allergic dermatitis taking into account current clinical guidelines with an emphasis on childhood.

Materials and Methods. This lecture presents consideration of modern principles of treatment of contact allergic dermatitis taking into account the specific features of pediatric practice. A non-systematic literature review was conducted. Pharmacological mechanisms of main medications used are discussed. Focus is based on rational skin therapy. Besides information is given about topical glucocorticosteroids and principles in choosing of concrete group and formulation of them. Also characteristics of topical calcineurin inhibitors are given, and their role in treatment of contact allergic dermatitis is explained. In addition, mechanism of the "vicious circle" during secondary infection and treatment tactics are described.

Results. Increased prevalence of contact allergic dermatitis in children depends primarily on household contact with chemicals and metals, as well as on the use of topical medications. This should be taken into account in prescription of elimination regime. Choice of the class and the formulation of topical corticosteroids should be made differentially taking into account the age, structural features of the child's skin, its sensitivity in different areas and the stage of the inflammatory process. Based on indications topical calcineurin inhibitors might be used in treatment of contact allergic dermatitis especially in pediatric practice. They are characterized by the absence of those side effects which are common during use of topical corticosteroids. Secondary infection which is quite often observed in CAD in childhood requires timely administration of antiseptics and combined topical medications containing corticosteroids, antibiotics and antifungal components.

Conclusion. Contact allergic dermatitis has good prognosis in case of implementation of elimination measures, adherence to treatment algorithm in accordance with clinical guidelines and age-based characteristics.

Keywords: contact dermatitis, contact allergic dermatitis, topical glucocorticosteroids, topical calcineurin inhibitors

Conflict of interests:
Author declares no conflict of interests.

For citation: Vasileva A.A. Principles of treatment of contact allergic dermatitis: features associated with children and adolescents. *Allergology and Immunology in Pediatrics*. 2025; 23 (2): 29–37. https://doi.org/10.53529/2500-1175-2025-2-29-37

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Принципы терапии аллергического контактного дерматита: особенности у детей и подростков

https://doi.org/10.53529/2500-1175-2025-2-29-37

УДК 616.5-001.1-08-053.2/.053.6
Дата поступления: 09.01.2024
Дата принятия: 23.05.2025
Дата публикации: 17.06.2025

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Аннотация

Актуальность. Аллергический контактный дерматит является одним из наиболее распространенных аллергических заболеваний кожи, в связи с чем высок научно-практический интерес к данной патологии. Увеличение роста аллергического контактного дерматита у детей и подростков объясняет актуальность решения проблемы лечения заболевания в этой возрастной группе.
Цель лекции. Целью данной лекции является рассмотрение современного подхода к лечению аллергического контактного дерматита с учетом актуальных клинических рекомендаций с акцентом на детский возраст.
Материалы и методы. Настоящая лекция представляет собой изложение современных принципов терапии аллергического контактного дерматита с учетом особенностей в детской практике. Проведен несистематический обзор литературы. Обсуждаются механизмы, лежащие в основе действия основных групп лекарственных препаратов. Уделяется внимание рациональной наружной терапии кожного воспалительного процесса. Рассматриваются топические глюкокортикостероиды и принципы выбора как конкретной группы данных препаратов, так и их лекарственной формы. Дается характеристика и объясняется место топических ингибиторов кальциневрина в терапии аллергического контактного дерматита. Описывается механизм «порочного круга» при вторичном инфицировании и рассматривается тактика лечения.
Результаты. Рост распространенности аллергического контактного дерматита у детей зависит прежде всего от бытового контакта с продуктами химической промышленности и металлами, а также от использования наружных лекарственных препаратов. Это следует учитывать при обеспечении элиминационных мероприятий. Выбор класса топических ГКС и формы препаратов следует осуществлять дифференцированно с учетом возраста, особенностей строения кожи ребенка, ее чувствительности на разных участках и стадии воспалительного процесса. В лечении АКД, особенно в детской практике, с учетом показаний могут быть использованы топические ингибиторы кальциневрина, не имеющие побочных эффектов, присущих ТГКС. Вторичное инфицирование, часто наблюдаемое при АКД у детей, требует своевременного назначения антисептиков и комбинированных топических препаратов, содержащих ГКС, антибиотики и антимикотики.
Заключение. Аллергический контактный дерматит имеет благоприятный прогноз при грамотно осуществляемых элиминационных мероприятиях, при соблюдении алгоритма лечения в соответствии с клиническими рекомендациями и с учетом возрастных особенностей.

Ключевые слова: контактный дерматит, аллергический контактный дерматит, топические глюкокортикостероиды, топические ингибиторы кальциневрина

Конфликт интересов:
Автор заявляет об отсутствии конфликта интересов.

Для цитирования: Васильева А.А. Принципы терапии аллергического контактного дерматита: особенности у детей и подростков. *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 29–37. https://doi.org/10.53529/2500-1175-2025-2-29-37

INTRODUCTION

Contact dermatitis is a fairly common inflammatory skin disease that occurs when the skin is directly exposed to various external factors and may have an acute or chronic course. There is known simple irritant contact dermatitis and allergic contact dermatitis (ACD). While simple irritant contact dermatitis has no immune mechanism, ACD is an allergic skin disease, the pathogenesis of which is based on a delayed-type hypersensitivity reaction (DTH)[1]. The most frequently mentioned contact allergens are: metals chromium, cobalt and nickel, rubber and rubber products, some medicines, disinfectants, formaldehyde, resins and a number of other substances [1, 2].

There is a rather high (about 16.5%) prevalence of ACD in children of different ages [3]. This is due, in particular, to the widespread use of chemical industry

[1] Clinical guidelines. Contact dermatitis. [internet]. 2024.

products in the home: detergents, cleaning agents, as well as contact with dyes used in the manufacture of children's clothing and toys. In children of the first year of life, ACD is mainly associated with the use of children's cosmetics and laundry detergents [4]. A high prevalence of ACD to nickel is noted in all age groups (about 10%). This may be due to contact with toys, stationery, hairpins, etc., and may be due to exposure to nickel. In adolescence, nickel-associated ACD is often associated with wearing metal jewelry made of nickel alloys, piercing products, contact with hardware, etc. Allergic contact dermatitis to various cosmetics is also more often observed in adolescents [5, 6]. Regardless of age, the cause of ACD in children may be contact with rubber products and medicines.

Clinical signs of ACD appear 10-14 days or more after the initial contact with the allergen. In the case of repeated contact with the allergen (hapten), 12-48 hours must elapse before symptoms appear. In situations of repeated skin exposure to neomycin sulfate, nickel, paraphenylenediamine and thixocortol pivalate, late delayed manifestations of ACD may occur, i.e. in this case several days later. The clinical symptoms of acute ACD are hyperemia, edema, and sometimes papules and vesicles at the site of contact with the allergen. In some cases, short-term, unexpressed areas of mottling may form (eczematized ACD). In chronic ACD there is stagnant erythema, infiltration, lichenification, and in exacerbation there is eczematization with mottling [7].

In some cases, systemic allergic contact dermatitis is observed, with localized or generalized cutaneous inflammation resulting from systemic re-exposure to the allergen. This variant of dermatitis has been described in sensitization to certain drugs, nickel, rosin, Peruvian balsam, parabens, cinnamon aldehyde, spices (cloves, cinnamon, nutmeg, cayenne pepper). The skin process may form both in places of previous localization of ACD and on previously unaffected areas and accompanied by general symptoms (headache, weakness, arthralgia, nausea, vomiting, diarrhea) [8].

SPECIFICS OF ELIMINATION MEASURES

Elimination measures to exclude or reduce contact with causative allergens are important in the management of patients with allergic diseases. Recommendations for elimination of the causative allergen play a crucial role in the management of patients with ACD. It is often not possible to achieve complete elimination in ACD because a large number of commonly used household and industrial products may contain substances that cause the disease. Therefore, when recommending elimination of contact allergens to the patient or the child's parents, it is important to outline the range of possible uses of these substances, which can be very extensive, making it difficult to achieve complete elimination.

When providing recommendations for patients, it should be considered that continued exposure to nonspecific skin triggers exacerbates the course of ACD and reduces the effectiveness of therapeutic interventions.

PHARMACOTHERAPY

Pharmacotherapy of ACD should be prescribed regarding the severity, stage of the inflammatory process and its prevalence, the patient's age, as well as the presence of comorbidities. In the external therapy of ACD, topical glucocorticosteroids (TGCS) remain the “gold standard” of anti-inflammatory external therapy [1]. Currently, they have no alternative in terms of both speed and severity of anti-inflammatory action [9]. In the course of therapy with TGCS, it is necessary to follow the instructions for the use of the drugs, including the frequency of their application to the skin, duration of use and age restrictions. TGCS classifications take into account the strength of their anti-inflammatory effect. The international classification implies division of all TGCS according to this criterion into 7 classes [8].

One of the main factors determining the efficacy of topical glucocorticosteroids is the rate of absorption of the drugs by different skin layers. There are two known ways of TGCS penetration into the skin: it can occur directly transepidermally (the main way) or through hair follicles, sweat or sebaceous glands. A number of factors determine the degree of skin permeability for TGCS: properties of the active components of the drug and its base, the place of application of the drug, skin condition, etc. The patient's age is

Table 1. **Topical corticosteroids which are used in treatment of allergic contact dermatitis in accordance with clinical guidelines and instruction to medication (author's table)**
Таблица 1. **Топические ГКС, рекомендованные к применению при АКД в соответствии с Клиническими рекомендациями и инструкциями по применению (таблица автора)**

International non-proprietary name	Activity group	Age
Clobetasol propionate 0,05 %, cream	Class 1 (very strong)	From 1 year
Betamethasone dipropionate 0,05 %, ointment, cream	Class 1 (very strong)	From 1 year
Mometasone furoate 0,1 %, ointment	Class 2 (strong)	From 2 years
Betamethasone valerate 0,1 %, ointment	Class 2 (strong)	From 6 months
Fluticasone propionate 0,005 %, ointment	Class 2 (strong))	From 10 years
Mometasone furoate 0,1 %, cream	Class 4 (moderate strength)	From 2 years
Methylprednisolone aceponate 0,1 %, cream, ointment, oily ointment, lotion	Class 4 (moderate strength)	From 4 months
Betamethasone valerate 0,1 %, cream	Class 5 (moderate strength)	From 6 months
Hydrocortisone butyrate 0,1 %, cream, ointment, emulsion	Class 5 (moderate strength)	From 6 months
Fluticasone propionate 0,05 %, cream	Class 5 (moderate strength)	From 10 years
Hydrocortisone acetate 1 % ointment	Class 7 (weak)	From 2 years

important, which is associated with the peculiarities of skin structure in children, affecting the absorption of the drug. The skin of the face, neck, folds (as well as other large folds) and groin area is characterized by high sensitivity to the action of TGCS [10, 11]. If inflammation in ACD is localized in these areas, the use of TGCS with a lower degree of activity is recommended [12, 13].

The depth of TGCS penetration into the skin depends on the form of the drug, which is selected regarding the stage of inflammation. Thus, in acute inflammation characterized by edema, vesicles, maceration and maceration, high skin permeability is observed. In this situation, there is the choice of products in the form of lotion, aerosol, cream and lipocrem depending on the specific skin manifestation. This is due to the fact that the lowest permeability is observed in drug solutions and lotion. If the drug is in the form of cream, its skin penetration will be greater than that of solution but less than that of ointment. Maximum dermal absorption of topical GCS is possible when using preparations in the form of ointment. Therefore, when choosing the form of TGCS in chronic dermatitis manifested by dry skin and lichenization, when there is difficult accessibility for penetration of topical GCS, it is advisable to choose ointment forms of preparations (ointment, oily ointment) for application to the skin. The ointment base of the preparation also contributes to moisturizing the stratum corneum of the epidermis, which, in turn, increases skin permeability [10]. The high fat content in the base of the preparation can provide an additional occlusion effect [14]. When choosing the form of topical GCS, the localization of the inflammatory process is also taken into account, which affects the penetration of the drug due to the peculiarities of the skin structure in different areas. In case of inflammation in the scalp, face and folds, preference should be given to aerosols, lotions, gels and creams that do not contain a fatty base [10].

Age-specific skin characteristics in children, among other criteria, are considered in the instructions for the drugs when determining the age barriers for prescribing specific TGCS, their dosage forms and mode of use[1] (Table 1).

Methylprednisolone aceponate 0.1% in the form of cream, ointment, emulsion can be used from 4 months of age.

Etamethasone valerate 0.1% (cream, ointment) is approved for use in children from 6 months of age, and betamethasone dipropionate 0.05% in the form of cream for the treatment of ACD - from the age of 1 year. Betamethasone dipropionate 0.05% in the form of a spray and mometasone furoate (cream, ointment 0.1%) can be used in children over 2 years of age.

Cream for external use clobetasol propionate 0.05%, according to the instructions, is allowed for use in children over 1 year of age.

Hydrocortisone butyrate 0.1% (ointment, cream, lipocrem, emulsion) is allowed for use from 6 months of age. According to the instructions, hydrocortisone acetate 1% in the form of ointment can be used from the age of 2 years.

[1] Clinical guideline. Contact dermatitis. [internet]. 2021.

Fluticasone propionate 0.05% cream is contraindicated for use in children under 10 years of age.

Safety of TGCS when administered in children is one of the key factors in selection of a particular drug and its dosage form.

Should be borne in mind that for the use of TGCS in children from the activity group "very strong": clobetasol propionate 0.05% (cream), betamethasone dipropionate 0.05% (ointment, cream, spray) - there should be strict indications. Great caution is required when prescribing the above drugs during the growth period in children. In the Clinical Guidelines for Contact Dermatitis there is an indication to avoid the use of clobetasol propionate 0.05 % in children, authorized according to the instructions for use from 1 year of age.

Regarding the nature and localization of the skin process in dermatitis, the child's age in the acute period of dermatitis, it is preferable to use TGCS of medium or strong activity. These groups of drugs effectively control the symptoms of inflammation, quickly restore the barrier function of the skin and thereby reduce the systemic absorption of drugs. It is indicated that short courses (3 days) of strong drugs are comparable in efficacy and safety to long courses (7 days) of weak TGCS. The duration of a continuous course of TGCS in children should be, on the one hand, sufficient to achieve the effect and at the same time, in order to ensure safety, minimized as much as the clinical situation allows. It is emphasized that in children the continuous course of this group of drugs should not exceed 2 weeks, and a gradual reduction in the frequency of their application to the skin is recommended if there is a significant reduction in inflammatory symptoms [14].

The group of topical calcineurin inhibitors (tacrolimus and pimecrolimus) used in the treatment of contact dermatitis deserves special attention.

These drugs may be the drugs of choice when inflammation is localized in the face, especially in children. Prolonged use of TGCS in the face can lead to a number of complications: skin atrophy, development of steroidal rosacea. The use of corticosteroids in the periorbital region may cause an increase in intraocular pressure. In such situations, replacement of TGCS with calcineurin inhibitors is justified. The use of tacrolimus and pimecrolimus in the treatment of contact dermatitis is indicated in the presence of contact hypersensitivity to TGCS [15, 16].

Topical calcineurin inhibitors belong to the class of ascomycin macrolactams with anti-inflammatory and immunosuppressive action. The drugs have high affinity for the skin, local immunotropic activity and high selectivity of anti-inflammatory action. Unlike corticosteroids, they do not affect the structure of the skin and, therefore, can not cause its atrophy. Topical calcineurin inhibitors are able to inhibit proliferation and activation of CD4+ T-lymphocyte-helper cells. In addition, they influence on nerve fibers, affecting the functioning of ion channels associated with the release of neuropeptides and substance P. The action of substance P is associated with a transient burning sensation after application of the drugs. These preparations are also characterized by short-term stimulation of excessive release of inflammatory factors with their subsequent depletion. These mechanisms explain the subsequent antipruritic effect of the preparations [15, 16, 17].

Having a more selective mechanism of action than TGCS, topical calcineurin inhibitors do not cause side effects inherent to TGCS. At the same time, their clinical efficacy has been described, in particular in the treatment of ACD [8, 15].

It should be noted that pimecrolimus (1% cream for external use) is contraindicated for use in children under 3 months of age. Tacrolimus (0.03% ointment) is approved for use in children from the age of 2 years, and in the form of 0.1% ointment it is contraindicated for use in children under 16 years of age.

The question of systemic glucocorticosteroids is raised in severe, widespread and systemic allergic contact dermatitis, when external therapy alone is ineffective. Dermatitis is considered widespread when more than 20% of the skin is affected. In these cases, systemic short-acting oral or parenteral GCS are administered depending on the severity of the skin process and body weight of the child: in the dose of prednisolone from 0.5 to 1 mg / kg (maximum 60 mg per day). Equivalent doses of other glucocorticosteroids may be used[1]. The course is 3-5-7 days. [6, 8]. The algorithm of systemic GCS withdrawal is carried out in each specific case in accordance with generally accepted rules depending on the course duration and drug dose.

[1] Allergology and Clinical immunology (Edition: clinical guidelines) / edited by R. M. Khaitova, N. I. Ilyina... C. 18.

In both simple contact dermatitis and ACD, excoriations and fissures are often observed in the inflamed area and secondary infection must be prevented or eliminated. These situations occur most often in pediatric ACD. The use of antiseptics, disinfectants and methylene blue can be considered for this purpose. For external application, a solution of fucorcin can be used. On the skin area treated in this way, after the liquid dries, you can use preparations in the form of ointments. Fucorcin is contraindicated in women during pregnancy, as well as during breastfeeding. The use of 1% aqueous solution of methylene blue is allowed during pregnancy and breastfeeding. The drug is authorized for use in children from the moment of birth[1].

In contact dermatitis (simple and allergic) against the background of itching, as a rule, excoriations are observed, which leads to the violation of skin integrity with the subsequent accession of secondary infection. In this case, the predominant bacteria are Staphylococcus aureus and group A hemolytic streptococci [18]. With secondary infection of simple irritant and ACD in the clinical picture there is an increase in erythema and the appearance of pustules. Precipitation boundaries are clear. Pronounced fine-platelet desquamation, as well as crusts of honey-yellow colour may appear in the inflammation area [19].

The formation of a "vicious circle" in case of secondary infection in skin diseases is of interest. Interleukins 31 and 33 (IL-31 and IL-33) are involved in the mechanism of skin itching and inflammation. In turn, skin scratching stimulates additional release of IL-33 from keratinocytes, which is also responsible for suppressing the production of protective skin proteins and, as a consequence, for disruption of the mechanical skin barrier [20]. The situation is aggravated in case of secondary skin infection. Infectious agents can induce IL-31 production by monocytes and macrophages, which leads to increased itching and skin damage due to scratching. This causes increased inflammation and bacterial colonization of the skin [21].

Considering the issues of secondary infection in dermatitis, it is necessary to separately touch on infections of fungal etiology. Patients with various skin diseases are at risk for the occurrence of mycoses. Mycotic infection in dermatitis for a long time remains undetected, often considered as a manifestation of the underlying disease, supports the skin inflammatory process, aggravating the course of the disease. Patients with various skin diseases are at risk of mycosis occurrence [21, 22].

In case of ACD complicated by microbial infection, timely use of combined topical medicines containing GCS in combination with an antibiotic (gentamicin, fusidic acid, neomycin, etc.) or GCS in combination with an antibiotic and antimycotic component (natamycin, clotrimazole, etc.) is indicated [8].

The following combinations of topical GCS and antibiotic are available: betamethasone + gentamicin; hydrocortisone + oxytetracycline, or hydrocortisone + chloramphenicol, or hydrocortisone + fusidic acid; betamethasone + fusidic acid. In contrast, the drugs containing topical GCS, antibiotic and antimycotic in their composition include: combination of betamethasone with gentamicin and clotrimazole or combination of hydrocortisone with neomycin and natamycin. When using combined agents containing TGCS, antibiotic and antimycotic, high concentrations of active substances in the focus of lesions in the skin area are provided. In this case, it is reasonable to recommend short courses of combined topical glucocorticosteroids (usually lasting 1 week).

Systemic antibiotics are indicated if there is no response to topical combination therapy and in cases of widespread bacterial infection on the skin[2].

The question of the advisability of using systemic antihistamines in ACD is often raised. There are no convincing data demonstrating the efficacy of H1-histamine receptor blockers in the treatment of ACD [8]. There are recommendations for their use to reduce pruritus. Clinical guidelines indicate the expediency of parenteral administration of systemic antihistamines, belonging to the first generation, in case of severe pruritus. In case of indications for the use of systemic antihistamines in children, preference should be given to oral non-sedative antihistamines of II generation as safer drugs[3].

Systemic blockers of H1-histamine receptors can be used to reduce the intensity of itching, but only as part of the complex therapy of allergic contact dermatitis.

[1] Clinical guideline. Contact dermatitis. [internet]. 2021.
[2] Allergology and Clinical immunology (Edition: clinical guidelines) / edited by R. M. Khaitova, N. I. Ilyina ... C. 18.
[3] Clinical guideline. Contact dermatitis. [internet]. 2021.

H1-histamine receptor blockers in forms for topical application (gels, creams, etc.) are not recommended for the treatment of ACD.

CONCLUSION

If elimination can be achieved, allergic contact dermatitis most often has a favorable prognosis. Thus, in case of timely elimination of contact with the identified causative allergen, clinical symptoms completely regress in 1-3 weeks [23]. Otherwise, the disease acquires a chronic course, in which, even after the elimination of the causative factor, the pathologic skin process may continue for a long time and require therapy in accordance with the peculiarities of the clinical picture in each case. However, chronic ACD in children is observed very rarely, as it is mainly associated with occupational factors, and it is not always possible to exclude contact with them. The modern approach to the therapy of ACD provides, first of all, the prescription of topical GCS. The choice of a specific drug and its dosage form is determined by the nature and stage of the inflammatory process. The key factor in the choice of topical GCS in pediatric practice is their safety. Topical calcineurin inhibitors, inferior in strength of anti-inflammatory effect to TGCS, but free of their side effects, can be used when indicated. Since in ACD there is often secondary infection, the use of antiseptics remains relevant, including for prophylactic purposes. In cases of ACD complicated by microbial infection, it is recommended to prescribe combined topical medications containing GCS in combination with antibiotic or antibiotic and antimycotic regarding frequent acceding fungal infection. As for the use of GCS in ACD, they are prescribed in severe, widespread and systemic allergic contact dermatitis.

ACD treatment algorithm is based on modern clinical guidelines, regarding individual approach to compel therapy of this common allergic skin disease.

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FINANCING SOURCE

Author declares that no funding was received for this study.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Автор заявляет об отсутствии спонсорской поддержки при проведении исследования.

AUTHOR'S CONTRIBUTION TO THE WORK

Alla A. Vasileva — data collection and analysis , writing the manuscript.

ВКЛАД АВТОРА В РАБОТУ

Васильева А. А. — сбор материала, анализ полученных данных, написание статьи.

Обзор / Review

Allergic diseases and childhood obesity: is there a relationship?

REV — обзорная статья

https://doi.org/10.53529/2500-1175-2025-2-38-49

date of receipt: 12.02.2025
Date of acceptance: 13.05.2025
Date of publication: 17.06.2025

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Resume. Over the past decades, the proportion of obese children has increased 4-fold. At the same time, there is an increase in allergic pathology in the children's population.
The aim is to present modern data on the relationship between childhood obesity and allergic diseases.
Materials and methods. A search was conducted for domestic and foreign literature on the relationship between various links in the pathogenesis of allergic pathology and obesity using the databases Scopus, Web of Science, PubMed, Google Scholar, eLibrary, Cyberleninka. The review includes studies published from January 2016 to January 2025.
Results. Data on the mechanical and inflammatory effects of obesity in relation to atopy in children are described. In addition, obesity is associated with increased production of inflammatory cytokines and adipokines, which supports low-activity systemic inflammation and increases the risk of exacerbations of allergic diseases. Allergic rhinitis, atopic dermatitis, food allergies, and chronic urticaria also appear to be associated with the chronic systemic low-activity inflammation characteristic of obesity. Vitamin D deficiency, characteristic of obesity, appears to play a role in the development of bronchial asthma and allergic rhinitis, while dyslipidemia and skin barrier defects may explain the link between obesity and atopic dermatitis.
Conclusion. Further research on the relationship between obesity and atopy is needed, confirming the role of adipose tissue in the development of allergic diseases, in order to develop new therapeutic strategies.

Keywords: obesity, allergy, atopic dermatitis, asthma, children

Conflict of interest:
The authors declare that there is no conflict of interest.

For citation: Belykh N.A., Lebedeva I.N., Piznyur I.V., Kotova P.O., Deeva Yu.V. Allergic diseases and childhood obesity: is there a relationship? *Allergology and Immunology in Pediatrics*. 2025; 23 (2): 38–49. https://doi.org/10.53529/2500-1175-2025-2-38-49

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Обзор / Review

Аллергические заболевания и детское ожирение: есть ли связь?

https://doi.org/10.53529/2500-1175-2025-2-38-49

УДК 616-056.3:616-056.52]-053.2
Дата поступления: 12.02.2025
Дата принятия: 13.05.2025
Дата публикации: 17.06.2025

Белых Н. А., Лебедева И. Н., Пизнюр И. В., Котова П. О., Деева Ю. В.

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Резюме. В течение последних десятилетий удельный вес детей, страдающих ожирением, увеличился в 4 раза. Параллельно в детской популяции отмечается рост аллергической патологии.
Цель — представить современные данные о взаимосвязи между детским ожирением и аллергическими заболеваниями.
Материалы и методы. Проведен поиск отечественной и зарубежной литературы о взаимосвязи различных звеньев патогенеза аллергической патологии и ожирения с использованием баз данных Scopus, Web of Science, PubMed, Google Scholar, eLibrary, Cyberleninka. *В обзор включены исследования, опубликованные с января 2016 года по январь 2025 года.*
Результаты. Описаны данные о механических и воспалительных эффектах ожирения в отношении атопии у детей. Кроме того, ожирение связано с повышенной выработкой воспалительных цитокинов и адипокинов, что поддерживает системное воспаление низкой активности и повышает риск обострений аллергических заболеваний. Аллергический ринит, атопический дерматит, пищевая аллергия и хроническая крапивница также, по-видимому, связаны с хроническим системным низкоактивным воспалением, характерным для ожирения. Дефицит витамина D, характерный для ожирения, по-видимому, играет определенную роль в развитии бронхиальной астмы и аллергического ринита, в то время как дислипидемия и дефекты кожного барьера могут объяснить связь между ожирением и атопическим дерматитом.
Заключение. Необходимы дальнейшие исследования взаимосвязи между ожирением и атопией, подтверждающие роль жировой ткани в развитии аллергических заболеваний, для разработки новых терапевтических стратегий.

Ключевые слова: ожирение, аллергия, атопический дерматит, бронхиальная астма, дети

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Белых Н.А., Лебедева И.Н., Пизнюр И.В., Котова П.О., Деева Ю.В. Аллергические заболевания и детское ожирение: есть ли связь? *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 38–49. https://doi.org/10.53529/2500-1175-2025-2-38-49

INTRODUCTION

Obesity and allergic diseases are a major public health burden today [1]. The World Obesity Federation predicts that by 2035, more than 1.5 billion adults and nearly 400 million children will be overweight and obese, and the global prevalence of childhood obesity will more than double between 2020 and 2035, from 10% to 20% among boys and 8% to 18% among girls [2].

At the same time, the prevalence of allergic diseases is also increasing significantly. Allergic rhinitis (AR) is the most common allergic disease, affecting 20 to 30% of adults and up to 40% of children in industrialized countries [3]. Atopic dermatitis (AtD) affects up to 12% of children and 7.2% of adults worldwide, and in Russia, according to the results of studies, the prevalence of AtD among children 7-8 years old varied from 5.5% to 49.2% depending on the region, and

among children 13-14 years old - from 3.3% to 45.3% [4, 5]. The prevalence of bronchial asthma (BA) in childhood is registered with a frequency from 6 to 9% in different countries of the world and has a steady tendency to increase. In Russia, according to a recent epidemiologic study, the prevalence of BA among adults is 6-8% in children and up to 1.5% in adults [6]. Also in recent decades, there has been a significant increase in the frequency of food allergy (FA) - up to 6.7% [5]. Up to 1% of the population in the USA and Europe suffer from chronic urticaria (CU) [7]. At the same time, there is increasing evidence that obesity raises the risk of developing allergic diseases [8].

OBJECTIVE of this review is to present current data on the association between childhood obesity and allergic pathology.

MATERIALS AND METHODS. A search of Russian and foreign literature on the relationship between various links in the pathogenesis of allergic pathology and obesity was conducted using Scopus, Web of Science, PubMed, Google Scholar, eLibrary, and Cyberleninka databases. *The review included studies published from January 1, 2015 to January 1, 2025 in English and Russian languages.*

RESULTS. Allergic diseases arise not only from the interaction of genetic factors, but also from external causes that may increase susceptibility to allergic diseases through epigenetic changes. In particular, obesity represents an external factor involved in immunologic changes leading to a switch of the immune system to a Th2 cytokine profile and increasing the risk of developing atopy [9]. However, studies on the association between obesity and atopy have conflicting results. Some data indicate a correlation between BMI and the prevalence of atopy, while other results demonstrate a lack of association between atopy biomarkers such as serum IgE levels and blood eosinophil counts with obesity [10].

Inflammation caused by an imbalance of immune cells in adipose tissue may be associated with decreased tolerance to allergens and damage to the intestinal barrier. Adipose tissue contains many immune cells: mast cells, Th cells, cytotoxic T cells (Tc), regulatory T cells (Treg), regulatory B cells (Breg), invariant natural killer cells (iNKT) and M2 macrophages, which maintain immune balance. Obesity increases the number of pro-inflammatory immune cells, which secrete large amounts of pro-inflammatory cytokines (TNF-α, IL-6, etc.) and decreases the number of anti-inflammatory Treg, while anti-inflammatory M2 macrophages turn into pro-inflammatory (Ml) macrophages. Large amounts of pro-inflammatory cytokines can activate the nuclear factor kappa B (NF-ϰB) signaling pathway, induce the production of pro-inflammatory cytokines, chemokines, etc. and exacerbate the pro-inflammatory immunological effect. TNFα also activates NF-ϰB, which can increase the permeability of the epithelial barrier, disrupting the tight junctions of intestinal epithelial cells [11].

Treg dysfunction is one of the important links in the development of allergic diseases, since Treg are able to inhibit the proliferation of Th cells, reduce allergen-specific IgE secretion and migration of T cells into tissues, limit the interaction of eosinophils, mast cells and neutrophils with resident tissue cells [11]. This leads to decreased tolerance to allergens, promotes differentiation of native CD4+ T cells (Th0) into Th2 cells, causing allergic reactions. Elevated circulating levels of adipose tissue-derived pro-inflammatory cytokines may impair the survival and/or maturation of circulating Treg cells.

Mast cells are effector cells, secrete inflammatory mediators, and in allergic reactions cause symptoms in the skin, respiratory tract, and digestive tract. Mast cells are abundant in adipose tissue and can interact with adipocytes to recruit inflammatory cells.

Adipose tissue secretes a variety of adipocytokines, including leptin, adiponectin, IL-6 and TNF-α etc., which are actively involved in metabolic homeostasis. In adipose tissue accumulation, adipocyte dysfunction and dysregulation of adipocytokines are noted, which can cause local or systemic effects, leading to pathological processes associated with inflammation.

Leptin activates CD4+ T cells, stimulates the secretion of proinflammatory cytokines (TNF-α, IL-6, IL-12), which, in turn, suppresses Treg activity. Adiponectin enhances fatty acid degradation, reduces

blood glucose levels and increases insulin sensitivity, has anti-inflammatory, antioxidant activity, and counteracts TNF-α expression in adipocytes and macrophages. In addition, adiponectin, the level of which is reduced in obesity, suppresses the synthesis of IL-10 secreted by macrophages and adipocytes. All these changes impair the immunoregulatory function of Treg, resulting in decreased antigen tolerance.

PPARγ DYSREGULATION AND ALLERGIC REACTION. Peroxysome proliferator-activated receptors (PPAR's) are a class of ligand-dependent nuclear receptors expressed in various organs and tissues, including adipose tissue. PPARγ is expressed in various immune cells, regulates genes involved in lipid metabolism, immune and inflammation-related genes, and exerts anti-inflammatory effects by inhibiting the expression of pro-inflammatory genes. The pro-inflammatory effects of adipose tissue may attenuate the anti-inflammatory effects of PPARγ by reducing its expression.

There is evidence that supplementation with ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) can alleviate inflammation by upregulating PPARγ expression [12]. The effect of PUFAs on PPARγ also mediates changes in adipocytokine levels. The reduction of PPARγ in adipose tissue in obesity may affect Treg activity. Because PPARγ is a key regulator of mast cell maturation, decreased PPARγ expression in obesity accelerates mast cell differentiation, and increased mast cell activation may lead to intestinal barrier damage and increased risk of food allergy through the secretion of more tryptase.

OBESITY AND BRONCHIAL ASTHMA. Epidemiologic studies in recent years have demonstrated an association between BA and obesity. Although the mechanism of this relationship from the pathophysiologic point of view is not yet fully understood, obesity has been shown to be a risk factor for BA [9]. According to some authors, obesity increases the risk of BA development by 2.7 times, and overweight - by 2 times compared to patients with normal body weight [5]. J. E. Lang et al. (2019) showed that the highest risk of obesity-associated asthma is observed in prepubertal children in the absence of AR. The authors hypothesized that at this age, the likelihood of developing obesity-associated asthma would increase, especially in girls, while in boys this pattern is observed after 12 years of age [10]. But in a study conducted by R. Parlar-Chun et al. (2020), with the participation of 995 children, there was no association between childhood obesity and the severity of asthma course, resulting in prolonged hospitalization and intensive care [13].

L. B. Orriëns et al. (2020) suggested that overweight/obese children with BA have a high risk of intentional discontinuation of inhaled corticosteroid therapy, which, in turn, may lead to an increased frequency of asthma exacerbations [14]. An analysis of 16 European cohorts involving 21,130 children aged 3 to 8 years demonstrated that persistent wheezing and early onset of BA are associated with an increased risk of obesity [8].

The association between BA and obesity can be explained partly by mechanical factors and partly by the presence of chronic low-grade inflammation due to obesity. In some patients, obesity precedes asthma; in others, BA precedes obesity. This suggests that BA or its therapy may be a risk factor for obesity [15]. Bronchial asthma associated with obesity is more difficult to control. Patients tend to have more frequent exacerbations and have a lower quality of life [16]. Various studies show that obesity-associated BA differs from the classical phenotype, demonstrating a non-Th2-mediated response. BA exacerbations in obese patients are often characterized by a reduced response to baseline therapy [5]. This phenotype of BA is characterized predominantly by women and is accompanied by the absence of eosinophilic airway inflammation [5]. A significant negative correlation between the percentage of eosinophils in induced sputum and BMI and waist circumference was found, which may indicate the role of visceral fat in the maintenance of non-eosinophilic airway inflam-

mation, typical of obese individuals.

Several studies have focused on the association between BMI and exhaled nitric oxide (FeNO) concentration with opposite results. Some authors describe a positive relationship between FeNO concentration and BMI, concluding that FeNO may be a systemic link between airway inflammation and obesity. Separate studies demonstrate a negative correlation between BMI and FeNO in patients with obesity-associated asthma [5].

A diet rich in carbohydrates and saturated fatty acids and low in fiber and antioxidants increases the risk of obesity and respiratory symptoms [17]. Vitamin D deficiency may also increase the risk of BA in obese patients [18]. Dyslipidemia and insulin resistance (IR) are associated with impaired forced vital capacity of the lungs (FVC) and the severity of BA. Insulin is a trophic stimulus for lower airway smooth muscle cells; it promotes laminin production, which increases airway hyperresponsiveness by stimulating parasympathetic innervation, thereby contributing to airway obstruction. High levels of total cholesterol and low-density lipoprotein are more common in children with obesity-associated BA and are associated with impaired lung function [19]. However, the exact mechanism by which dyslipidemia affects lung function is not yet known.

Maternal obesity before and during pregnancy also appears to play a role in the development of BA in children later in life. In a study of the effect of maternal diet on bronchial hyperresponsiveness in adult offspring in a mouse model, it was found that maternal diet during pregnancy, rich in saturated fatty acids, plays a key role in the development of airway hyperresponsiveness in the offspring [5]. The increased risk of allergic reactions in children born to obese mothers appears to be due to excessive synthesis of pro-inflammatory cytokines caused by excess adipose tissue. Such changes are probably the result of long-term changes in the expression of miR-155 and miR-133b microRNAs [10]. In addition, environmental factors play a role: various studies show that air pollution and passive smoking are independent risk factors for the development of both asthma and obesity in children [20]. Impaired lung development and growth also play a role: obese children have increased lung volume relative to airway diameter ("dysanapsia"), as reflected by a lower ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC), despite normal FEV1 and FVC values. Dysanapsia is associated with decreased airway patency, more frequent exacerbations of BA, and use of systemic glucocorticoids in obese children [21].

Mechanical factors also play a role: obesity causes significant changes in lung and chest mechanics that cause asthma-like symptoms such as dyspnea, wheezing and airway hyperresponsiveness. Excess fat mass in the chest and abdomen reduces functional residual lung capacity (FRLC) [17]. It is also associated with decreased FVC and FEV1 [19-22]. Breathing with reduced respiratory volume due to excess fat in the thorax and abdomen leads to decreased lung volume, causing alveolar hypoventilation and increased airway resistance. These phenomena, in turn, cause airway hyperresponsiveness, leads to increased respiratory rate and increased chest elasticity. Collectively, all these changes lead to stiffness of airway smooth muscle in obese individuals, which leads to a decrease in bronchodilator effect [5].

In addition, the function of immune cells is also altered: traditionally, BA and other atopic diseases are thought to be associated with type 2 Th and increased levels of IgE and eosinophils. In obesity, the functions of adaptive and innate immune cells are impaired. Some studies show suppression of Th2 function in obese patients, i.e., the immune response shifts toward Th1 type [23]. Visceral inflammation with increased numbers of pro-inflammatory macrophages (M1) is also observed in patients with obesity-associated asthma and may determine systemic inflammation and the severity of BA [5]. In obese patients, oxidative stress, cell necrosis products, and excess free fatty acids lead to polarization toward the M1 phenotype, while the number of anti-inflammatory M2 macrophages decreases [24].

Eosinophil function is also altered in obesity. While the number of submucosal eosinophils is increased in obese patients with BA, the number of eosinophils in peripheral blood and sputum is not increased in obesity. All these aspects may explain why current drugs used in the therapy of BA, including corticosteroids, leukotriene inhibitors, and biologics that affect Th2 response and eosinophils, are less effective in patients with obesity-associated BA [19].

Adipose tissue mediators also play a role in the pathogenesis of BA. Adipose tissue is an active endocrine organ that can influence the functions of other organs, as well as a source of proinflammatory cytokines, chemokines, and growth factors [5]. Obesity is associated with increased production of inflammatory cytokines (IL-6, IL-1β and TNF-alpha), leading to low activity systemic inflammation and increased risk of frequent exacerbations of BA [8, 19]. High circulating IL-6 levels are associated with poor control of BA, and inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen are elevated in patients with obesity-associated asthma compared to patients with non-obese BA [5, 19].

In recent years, several cytokines produced by adipose tissue, the so-called adipokines, have been identified. Adipokines play a crucial role in energy homeostasis as well as in inflammatory and immune responses, supporting inflammation [24]. Leptin and resistin are pro-inflammatory cytokines, while adiponectin has anti-inflammatory properties. Leptin levels are positively correlated with adipose tissue mass, so it is considered one of the factors explaining the association between obesity and BA. The most important role of leptin is to suppress appetite by inhibiting the hypothalamic nuclei that stimulate hunger and activating the nuclei that induce the feeling of satiety. However, in obesity, patients develop leptin resistance with decreased sensitivity to anorexinergic stimuli. Leptin dysfunction leads to hyperphagia, rapid weight gain, and IR. Leptin stimulates neutrophil activation and chemotaxis, oxygen radical release and survival of macrophages, eosinophils, basophils and natural killer cells. Leptin and IL-6 decrease the activity of regulatory T lymphocytes (Treg), reducing immunologic tolerance to antigens, thereby increasing the risk of developing allergies and other immune-mediated diseases [25]. Adiponectin reduces the risk of AD, independent of BMI [25]. In macrophages, adiponectin promotes polarization of the M2 phenotype, decreases TNF-alpha secretion and enhances phagocytic activity. In addition, adiponectin stimulates the release of IL-10, one of the major anti-inflammatory cytokines that plays a key role in regulating the immune response and increasing insulin sensitivity. The role of resistin in the development of BA in obesity remains unclear. Some studies have found higher levels of resistin in patients with BA, and correlation of its levels with worsening disease control, while other authors have suggested that resistin prevents the development of BA [25]. Thus, adipokines play a key role in realizing the association between obesity and changes in the immune response, resulting in poorly expressed systemic inflammation and decreased immune tolerance. Body weight reduction combined with lifestyle modification effectively suppresses the level of serum markers of inflammation and IR in obese children and adolescents, resulting in improved BA control, lung function parameters and quality of life of patients [5, 25].

OBESITY AND ALLERGIC RHINOCONJUNCTIVITIS . Several studies have investigated the relationship between obesity and AR and rhinoconjunctivitis. A meta-analysis of 30 observational studies by Zhou J. et al. (2020) found a statistically significant association between obesity and the risk of AR in children [26]. The authors suggested that this association may be due to a common inflammatory etiology. Immunologic changes caused by obesity may lead to decreased immunologic antigen tolerance, thereby increasing the risk of developing AR. However, other factors, such as vitamin D deficiency, may also contribute to the association between obesity and AR: obese patients with vitamin D deficiency appear to have an increased risk of developing atopic diseases [5]. A positive correlation was found between obesi-

ty and atopic dermatitis and AR in adults, as well as a positive correlation between increasing BMI and the prevalence of AR and conjunctivitis, especially among young women and children [5]. M. W. Han et al. (2021) investigated the mechanisms by which obesity can influence the severity of AR. The authors analyzed the levels of leptin and inflammatory biomarkers in serum and found that the level of IL-1β, a biomarker of active inflammation, was significantly higher in patients with AR than without AR, as well as in obese individuals than in the group of people with normal body weight. Data analysis showed that leptin levels were associated with increased IL-1β expression in children with AR. In multivariate analysis, elevated leptin level and high IL-1β expression were found to be significant risk factors for the development of moderate to severe persistent AR [27].

Also, recent studies suggest a role for leptin in the development of AR in obese children. Leptin appears to increase the expression of innate lymphoid cell type 2 (ILC2), which may be involved in the development of AR [28]. These results suggest that obesity is a significant risk factor for exacerbations and severity of AR course. Allergic rhinitis is often a prerequisite for the subsequent development of AD (the so-called "atopic march"). Therefore, it becomes extremely important to control body weight to prevent the development of AR and subsequent BA [28].

OBESITY AND CHRONIC POLYPOUS RHINOSINUSITIS (CPRS). In recent years, several studies have been published to evaluate the association between obesity and CRPS. In a recent prospective population-based study conducted in Norway (2013-2018) involving 5769 patients, the authors found that the likelihood of developing CPRS was 53% higher in the obese group compared with the normal weight group [29]. Thus, BMI seems to be an important risk factor for the development of CPRS and should be taken into account in therapy. In a cross-sectional study by S. Nam et al. analyzed data from 32,384 patients aged 19 to 86 years and found that the prevalence of CPRS was higher in obese patients than in those with normal body weight [30].

In patients with asthma, CPRS is associated with increased eosinophilic airway inflammation and worsening lung function as measured by spirometry. The shared pathophysiology of CPRS and BA has important implications for the therapy of these conditions and provides a rationale for systemic therapy with new biologic agents targeting common Th2 inflammatory processes, such as dupilumab and omalizumab [31].

OBESITY AND ATD. A significant correlation was found between high BMI and AtD in children. In addition, obese children are significantly more likely to have a severe course of the disease. There is also evidence that prolonged obesity (more than 2.5 years) in early childhood is a modifiable risk factor for childhood AtD, while short-term obesity does not increase the risk of developing ATD. This suggests that rapid reduction of body weight is an important non-pharmacologic intervention for the prevention and treatment of AtD in children [32]. Chronic sluggish inflammation caused by excess adipose tissue is probably involved in the pathogenesis of AtD, and increased leptin expression and decreased adiponectin expression in obese patients may contribute to the pathogenetic link between obesity and AtD [33, 34]. A. K. Jaworek et al. (2020), while evaluating the levels of various adipokines in the blood of adult patients with normal body weight, suffering from chronic AtD since childhood, found increased levels of leptin and decreased levels of adiponectin in patients with AtD compared to healthy people. The level of adiponectin was negatively correlated with the severity of the disease [35]. However, the direct role of adipokines in the pathogenesis of AtD is still not fully understood. S. P. Bapat et al (2022) studied 2 mouse models of AtD and found marked differences in the immune response in lean and obese mice. Obesity transformed the classic Th2-dependent inflammation, into a more severe form of the disease with a predominance of Th17 inflammation. The authors also observed a different response to biological therapies targeting Th2 cytokines, which protected lean mice but worsened the condition in obese mice [36]. This may be impor-

tant for the development of effective treatments for children with obesity and allergic diseases.

Another mechanism that may explain the association between obesity and AtD is related to changes in lipid profile. A recent study by J. H. Kim et al. (2022) showed that children with AtD had significantly higher levels of total cholesterol and triglycerides, and this is associated with the AtD index (SCORAD) indicating the involvement of dyslipidemia in the pathogenesis of pediatric AtD [37]. It is also believed that mechanical factors such as skin maceration and stretch marks, often observed in obese patients, may also contribute to the development of AtD. Excess subcutaneous adipose tissue may adversely affect epidermal barrier function, as obese children have significantly higher rates of transepidermal water loss through the skin than normal body weight [5]. This suggests that obesity may exacerbate the course of AtD by compromising the integrity of the skin barrier, thereby facilitating transdermal penetration of allergens, leading to AtD. Further prospective cohort studies are needed to confirm the association between AtD and obesity.

OBESITY AND FOOD ALLERGY. Various studies show that obesity may contribute to the increase in the prevalence of FA in children. In a study conducted by K. Hayashi et al. (2021) in Japan, an analysis of data from 1,772 children revealed that in girls, excess weight was statistically significantly associated with FA (OR 1.99, p = 0.046), while in boys, no such association was found [38].

Dietary lipids can affect innate immune function and antigen presentation to adaptive immune cells. Lipids appear to alter the immunostimulatory properties of proteins and affect their absorption in the intestine, thereby altering the bioavailability of allergens [39]. A correlation has been found between CRP and total IgE levels, atopy, and food hypersensitivity [5]. This result suggests that the presence of low-grade inflammation in obese children may contribute to the development of FA. Some authors hypothesize that damage to the gastrointestinal barrier caused by a high-fat diet, hyperglycemia, and chronic systemic low-grade inflammation may explain the link between obesity and FA [40]. However, the pathophysiological mechanisms underlying this phenomenon have not yet been fully studied. L. Torres et al. (2023), in a study of changes in the intestinal mucosa in mice with alimentary obesity, found that they had increased permeability and reduced numbers of intraepithelial Tregs, and after oral administration of ovalbumin, tolerance did not develop, but a stronger reaction to ovalbumin was observed [41]. In addition, changes in the intestinal microbiota also play an important role in the development of obesity and FA. Further prospective studies are needed to identify the causal link between obesity and FA.

OBESITY AND CHRONIC URTICARIA. An Italian study analyzed the influence of various risk factors associated with CU and showed that the risk of developing CU was statistically significantly higher in obese patients. Chronic low-grade systemic inflammation in obesity may reduce immunological tolerance to antigens, thereby increasing the risk of CU [42]. There is evidence that central obesity is more common in patients with CU and correlates significantly with levels of TNF-alpha, total serum IgE, and eosinophil cationic protein [5]. However, further research is needed to confirm these findings and the possible link between obesity and the onset of CU.

CONCLUSIONS. Obesity is one of the risk factors for developing allergic diseases and, at least in part, is responsible for their recent increase. Disorders of innate and acquired immunity in obese patients also affect the development and severity of asthma. Polarization of the immune response towards Th1 and Th17 and an increase in the number of pro-inflammatory macrophages (M1) lead to an increase in the severity of asthma and explain the low effectiveness of basic therapy in patients with obesity-associated asthma. Excess body weight is associated with increased production of inflammatory cytokines (IL-6, IL-1β, and TNF-alpha) and adipokines (leptin and resistin), which leads to the formation of chronic systemic inflammation and increases the risk of BA exacerbations. However, the exact mechanism linking obesity and other atopic diseases remains unclear. Vitamin D deficiency appears to play a role in the development of

AR, while dyslipidemia and skin barrier defects may explain the link between obesity and AtD. Therefore, further research is needed on the association between obesity and atopic diseases to clarify the role of adipose tissue in the development of allergic diseases for the development of new therapeutic strategies.

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FUNDING SOURCES

The authors declare no sponsorship.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки.

THE AUTHORS' CONTRIBUTION TO THE WORK

Nataliya A. Belykh — conceptualization, writing — review & editing — preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision — including pre- or post-publication stages.

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Inna N. Lebedeva, Yulia V. Deeva — writing — review & editing.

ВКЛАД АВТОРОВ В РАБОТУ

Белых Н. А. — разработка концепции, подготовка текста — оценка и редактирование.

Пизнюр И. В., Котова П. О. — проведение исследования.

Лебедева И. Н., Деева Ю. В. — подготовка текста.

Оригинальная статья / Original article

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

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-2-50-56

Date of receipt: 23.10.2024
Date of acceptance: 02.04.2025
Date of publication: 17.06.2025

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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.

For citation: Khramova R. N. The relationship of serum IL-18 levels with body mass index, the presence of obstructive disorders in children and adolescents with bronchial asthma. *Allergology and Immunology in Pediatrics*. 2025; 2: 23 (2): 50–56. https://doi.org/10.53529/2500-1175-2025-2-50-56

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Оригинальная статья / Original article

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

https://doi.org/10.53529/2500-1175-2025-2-50-56

УДК 616.248
Дата поступления: 23.10.2024
Дата принятия: 02.04.2025
Дата публикации: 17.06.2025

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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.

Для цитирования: Храмова Р. Н. Взаимосвязь уровня сывороточного ИЛ-18 с индексом массы тела, наличием обструктивных нарушений у детей и подростков с бронхиальной астмой. *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 50–56. https://doi.org/10.53529/2500-1175-2025-2-50-56

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 = body weight (kg) / 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 Mastercreen pneumospirometer (Jaeger, Germany). The following parameters were evaluated when analyzing spirometry data:

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

FEV_1 (L/s) — forced expiratory volume in 1 second;

FEV_1/FVC — an index that is the main parameter of spirometry for diagnosing obstructive disorders.

Spirometry data were measured in absolute values and the FEV_1/FVC ratio was calculated.

The FEV_1/FVC z-score was used to diagnose obstructive disorders, with z-score values < −1,645 [11].

In addition, z FVC, z FEV_1 and z FEV_1/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 [Q_1; Q_3], where Me is the median, [Q_1; Q_3] 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

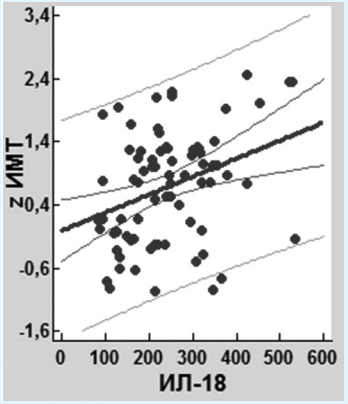
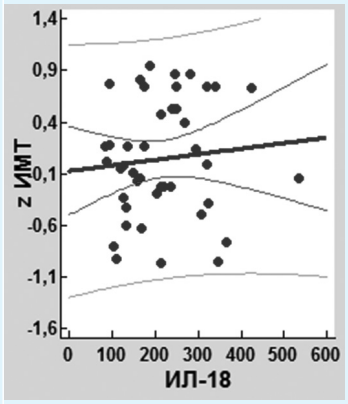
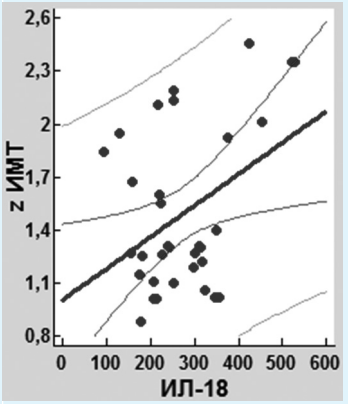
Patients with "low/normal body weight" and "overweight/obesity" were comparable in terms of gender and age (Table 1). The parameters z Height and z BMI were statistically significantly higher in patients who were overweight and/or obese, $p < 0.05$. z FEV1 values were statistically significantly higher, $p = 0.032$, 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 lowerFEV1 [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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FINANCING SOURCE

This study was not supported by any external sources of funding

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

THE AUTHOR' CONTRIBUTION TO THE WORK

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

ВКЛАД АВТОРА В РАБОТУ

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.

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

Исследование было одобрено Этическим комитетом Приволжского исследовательского медицинского университета (протокол № 13 от 10.10.2016 г.). Все участники и все лица, осуществляющие первичный уход, дали письменное информированное согласие.

A clinical case of community-acquired pneumonia of mycoplasmic etiology complicated by spontaneous mediastinal emphysema in a child with bronchial asthma

RAR — научная статья

https://doi.org/10.53529/2500-1175-2025-2-57-64

Check for updates

date of receipt: 12.02.2025
Date of acceptance: 11.05.2025
Date of publication: 17.06.2025

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Abstract

Introduction. In the period from October to December 2024, there was an increase in cases of community-acquired pneumonia in children caused by *Mycoplasma pneumoniae* in the Republic of Bashkortostan, which has important epidemiological and clinical consequences. Mycoplasma infections have a cyclical pattern of epidemics, frequent outbreaks in organized groups, and a significant seasonal pattern, which makes children particularly vulnerable. In children with bronchial asthma, mycoplasma infection can worsen the course of the disease, contributing to bronchial hyperreactivity and complications such as spontaneous mediastinal emphysema.

Objective. The aim is to perform a clinical and pathogenetic analysis of the course of community-acquired pneumonia caused by *Mycoplasma pneumoniae* in a child with bronchial asthma complicated by spontaneous mediastinal emphysema.

Presentation of the clinical case. The case of a 15-year-old boy with bronchial asthma and polyvalent sensitization, who developed community-acquired pneumonia of mycoplasmic etiology with a complication in the form of spontaneous mediastinal emphysema, is presented. The clinical picture of the disease included a dry cough, chest pain, difficulty breathing, and fever. The laboratory confirmed the diagnosis of mycoplasma pneumonia with a positive PCR result for *Mycoplasma pneumoniae*. X-ray examination revealed signs of inflammation and emphysema. Complex therapy included antibiotics, anti-inflammatory drugs and inhalation therapy, which contributed to the positive dynamics and improvement of the patient's condition.

Conclusion. The presented clinical case illustrates the specific course of community-acquired pneumonia of Mycoplasma etiology in a child with bronchial asthma complicated by spontaneous mediastinal emphysema. The combination of chronic airway inflammation and atypical bacterial infection contributed to the development of a severe complication. Timely diagnosis, including pathogen identification, comprehensive antibacterial and anti-inflammatory therapy, as well as maintenance of baseline asthma treatment, ensured a favorable clinical outcome and prevented adverse events.

Keywords: bronchial asthma, *Mycoplasma pneumoniae*, spontaneous emphysema of the mediastinum, children

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

For citation: Fayzullina R.M., Chernyshova A. E., Gafurova R. R., Golubyatnikov V. B. A clinical case of community-acquired pneumonia of mycoplasmic etiology complicated by spontaneous mediastinal emphysema in a child with bronchial asthma. *Allergology and Immunology in Pediatrics*. 2025; 23 (2): 57–64. https://doi.org/10.53529/2500-1175-2025-2-57-64

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Клинический случай внебольничной пневмонии микоплазменной этиологии, осложненной спонтанной эмфиземой средостения у ребенка с бронхиальной астмой

https://doi.org/10.53529/2500-1175-2025-2-57-64

УДК 616.24-6
Дата поступления: 12.02.2025
Дата принятия: 11.05.2025
Дата публикации: 17.06.2025

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Аннотация

Введение. В период с октября по декабрь 2024 года в Республике Башкортостан наблюдалось увеличение случаев внебольничной пневмонии у детей, вызванной *Mycoplasma pneumoniae*, что имеет важные эпидемиологические и клинические последствия. Микоплазменные инфекции обладают цикличностью эпидемий, частыми вспышками в организованных коллективах и значительным сезонным характером, что делает детей особенно уязвимыми. У детей с бронхиальной астмой микоплазменная инфекция может усугубить течение заболевания, способствуя бронхиальной гиперреактивности и осложнениям, таким как спонтанная эмфизема средостения.

Цель. Клинико-патогенетический анализ течения внебольничной пневмонии, вызванной *Mycoplasma pneumoniae*, у ребенка с бронхиальной астмой, осложненной спонтанной эмфиземой средостения.

Изложение клинического случая. Представлен случай 15-летнего мальчика с бронхиальной астмой, поливалентной ремиссибилизацией, у которого развилась внебольничная пневмония микоплазменной этиологии с осложнением в виде спонтанной эмфиземы средостения. Клиническая картина заболевания включала сухой кашель, боль в груди, затрудненное дыхание и повышенную температуру тела. Лабораторно подтвердился диагноз микоплазменной пневмонии с положительным результатом ПЦР на *Mycoplasma pneumoniae*. При рентгенологическом исследовании обнаружены признаки воспаления и эмфиземы. Комплексная терапия включала антибиотики, противовоспалительные препараты и ингаляционную терапию, что способствовало положительной динамике и улучшению состояния пациента.

Заключение. Представленный клинический случай иллюстрирует особенности течения внебольничной пневмонии микоплазменной этиологии у ребенка с бронхиальной астмой, осложненной спонтанной эмфиземой средостения. Сочетание хронического воспалительного заболевания дыхательных путей и атипичной бактериальной инфекции способствовало формированию тяжелого осложнения. Своевременная диагностика, включая верификацию возбудителя, комплексная антибактериальная и противовоспалительная терапия, а также поддержание базисного лечения астмы обеспечили положительную клиническую динамику и предотвращение неблагоприятных исходов.

Ключевые слова: бронхиальная астма, *Mycoplasma pneumoniae*, спонтанная эмфизема средостения, дети

Конфликт интересов:
Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Файзуллина Р. М., Чернышова А. Е., Гафурова Р. Р., Голубятников В. Б. Клинический случай внебольничной пневмонии микоплазменной этиологии, осложненной спонтанной эмфиземой средостения у ребенка с бронхиальной астмой. *Аллергология и иммунология в педиатрии*. 2025; 23 (2): 57–64. https://doi.org/10.53529/2500-1175-2025-2-57-64

INTRODUCTION

Between October and December 2024, the Republic of Bashkortostan saw an increase in the incidence of community-acquired pneumonia among children and adolescents caused by the atypical pathogen Mycoplasma pneumoniae. Mycoplasma infections are characterized by epidemic outbreaks with a cycle of 3–7 years, spreading across large regions and individual countries [1].

Mycoplasma pneumoniae is transmitted by airborne droplets, but due to its low survival rate in the external environment, infection is only possible through close contact with patients who have clinically pronounced or subclinical forms of the disease. This determines one of the key epidemiological features of respiratory mycoplasmosis — the spread of infection in organized groups, especially in closed institutions (boarding schools, orphanages) [2]. The incidence of the disease is highly seasonal, peaking in the fall and winter, which contributes to the active spread of infection among children attending educational institutions. During this period, *Mycoplasma pneumoniae* becomes the leading etiological agent of community-acquired pneumonia in schoolchildren, being detected in 40–60% of cases, and in closed communities this figure can reach 70% [3, 4]. The transmission of *Mycoplasma pneumoniae* is slow — the incubation period is 1–3 weeks, and in some cases reaches 4 weeks. In addition to organized groups, there are also cases of infection within families, which is due to close domestic contact. However, unlike other respiratory infections, the spread of *Mycoplasma pneumoniae* within families is slow. [5].

The clinical manifestations of mycoplasma infection vary from asymptomatic to severe forms. *Mycoplasma pneumoniae* often causes atypical community-acquired pneumonia, which can be severe in children. The infection also plays a significant role in the pathogenesis of bronchial asthma, provoking its exacerbations and increasing the risk of complications. [6, 7].

In bronchial asthma, mycoplasma infection exacerbates chronic inflammation of the respiratory tract, induces bronchial hyperreactivity, suppresses γ-interferon production, and disrupts mucociliary clearance. This creates favorable conditions for the persistence of the pathogen and the progression of the disease. [8, 9].

In addition to damaging the bronchial tree, *Mycoplasma pneumoniae* has a pronounced effect on the interstitial tissue of the lungs. Activation of innate and adaptive immunity is accompanied by the release of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines, which contributes to the intensification of the inflammatory process, increased vascular permeability, the development of edema, and cellular infiltration. Prolonged inflammation can stimulate fibroblast activity, increasing the risk of pulmonary fibrosis [10].

In patients with bronchial asthma, mycoplasma infection can lead to the development of subcutaneous emphysema, which is associated with structural changes in lung tissue. Rupture of the alveoli with subsequent migration of air into the interstitial space may be caused by inflammatory damage to the alveolar walls, barotrauma due to intense coughing, or destruction of the bronchial epithelium by an infectious agent. The combination of these factors exacerbates respiratory failure and reduces the effectiveness of supportive therapy. [11].

Thus, *Mycoplasma pneumoniae* in children with bronchial asthma contributes to the intensification of inflammatory processes in the lungs, disruption of the integrity of the alveolar-capillary membrane, and an increased risk of subcutaneous emphysema. This underscores the need for early diagnosis and a comprehensive approach to treatment.

OBJECTIVE: present a clinical case of community-acquired pneumonia of mycoplasmal etiology in a child with bronchial asthma complicated by spontaneous mediastinal emphysema, with an analysis of pathogenetic aspects, the effect of Mycoplasma pneumoniae on the course of respiratory pathology, and factors contributing to the development of complications.

CLINICAL CASE DESCRIPTION

The patient is a boy, born in 2010 (15 years old), delivered by an ambulance team to the emergency room of the city children's clinical hospital (CCCH, hereinafter referred to as the Clinic) in Ufa with the following referral diagnosis: "Community-acquired right-sided pneumonia, acute course, mild, uncomplicated, RF I. Bronchial asthma, allergic form, moderate severity, moderate exacerbation. Polyvalent sensitization (pollen, household, fungal)," with complaints of frequent, persistent, unproductive dry cough; sore throat and hoarseness; pain in the neck and chest,

worsening when breathing in and coughing; difficulty breathing during physical exertion; increased fatigue and body temperature up to 39 °C.

MEDICAL HISTORY. The child was born from the second pregnancy, which proceeded against the background of a threat of termination in the first trimester. The delivery was urgent, second, independent, without complications. Birth weight was 3400 g, length was 52 cm, Apgar score was 8/9 points. Breastfed for the first 6 months, then gradually transitioned to mixed feeding. Complementary foods were introduced on time, and tolerance of foods was satisfactory.

In early childhood, episodes of atopic dermatitis were noted. There is a family history of allergic diseases: the mother has hay fever. Living conditions are satisfactory: lives in a city apartment, no pets. Vaccinations were administered according to an individual schedule based on age and medical indications. Influenza vaccination was not administered due to parental refusal. Vaccination with Prevenar 13 was not administered. Since the age of 13, the child has been registered with a clinic with a diagnosis of bronchial asthma. At the time of admission to the hospital, he received anti-inflammatory therapy with a combination drug containing inhaled glucocorticosteroids and long-acting 2-agonists (IGCS/LABA) — fluticasone propionate/salmeterol at a dose of 125/25 mcg/dose per inhalation in the form of a metered dose inhaler as needed.

DISEASE HUSTORY. The child fell ill seven days ago. The illness began with a rise in body temperature to 37.3–37.5°C, a runny nose, sore throat, and headache. On the third day of the illness, a dry, persistent cough, difficulty breathing, and slight hoarseness appeared. Over the next two days, the condition worsened: dull chest pains appeared, intensifying with inhalation and coughing, radiating to the armpit area, and breathing difficulties increased, which led to a visit to a medical facility. On an outpatient basis, without consulting a pediatrician, the mother administered antiviral, inhalation, and symptomatic therapy, but no positive dynamics were observed with this treatment. On the seventh day after the onset of the disease, the patient was examined by a pediatrician at his place of residence. Given the epidemiological history and worsening symptoms, it was decided to refer the patient for inpatient treatment for further examination and to prescribe the necessary therapy.

The epidemiological history shows that the patient has a younger sister, aged 6, who attends kindergarten. Three weeks ago, she had mycoplasma pneumonia, which was confirmed by laboratory tests: *Mycoplasma pneumoniae* was detected in a throat swab using PCR. In addition, the sister underwent serological testing (ELISA), the results of which confirmed the presence of specific antibodies to *Mycoplasma pneumoniae*. Cases of infection among other children have been reported at the childcare facility she attends.

The child had no injuries or bruises.

CLINICAL DATA. On admission: height—168 cm, body weight—51 kg (BMI 18.07). Body temperature—37.8 °C, respiratory rate—24 per minute, heart rate—102 beats per minute, blood pressure — 106/62 mm Hg, SpO2 — 95%. General condition upon admission — moderate severity. The child is active. Skin is pale, warm, with slight periorbital and perioral cyanosis, which intensifies with coughing and physical exertion. Nasal breathing is difficult, with mucous-serous discharge. The pharynx is moderately hyperemic, tonsils are loose and clean. Nasal breathing is free. The chest participates evenly in the act of breathing. Shortness of breath is expiratory in nature. Palpation above the jugular notch and in the subclavian areas reveals an area of subcutaneous emphysema (up to 60 cm²). Palpation of the chest reveals slight tenderness and a slight feeling of tension in the neck. Percussion over all lung fields reveals a boxy percussion sound, with shortening noted on the right. Breathing is stiff, with prolonged exhalation, dry rales are heard, scattered throughout all lung fields, weakened in the lower right sections, where small-bubble wet rales and crepitus are also heard. Auscultation of the patient reveals a positive Hammann's sign (crepitus in the precordial region, synchronous with heart contractions, intensifying on inspiration in the supine position). Heart sounds are rhythmic, slightly muffled. The abdomen is soft and painless. Stool is formed and regular.

Laboratory test results: complete blood count at the time of hospitalization: leukocytosis with a left shift in the leukocyte formula (WBC 12.7 × 109/L, NEUT 59% (eosinophils 52%, neutrophils 7%), increased ESR (24 g/L). In the general urine analysis, coprogram, biochemical blood analysis, and coagulogram — no pathology.

Increase in CRP levels: 13 mg/l, PCT: 0,024 ng/ml.

Overview X-ray of the chest (frontal and lateral projection): moderate reduction in lung field transparency, small focal shadows in the lower right lung field. Lung pattern is enhanced due to vascular-interstitial component, enriched. Lung roots are densified. The median shadow is not displaced, the contours are clear and even. The heart is not enlarged in cross-section. The domes of the diaphragm are clear and even. The sinuses are free, with thickening of the transverse interlobar fissure on the right.

Based on the complaints, medical history, and objective data, spontaneous mediastinal emphysema was suspected. A CT scan of the chest was performed. Conclusion: multiple areas of air were found in the neck, subclavian regions, and mediastinum. The lungs are airy, adjacent to the chest, and the density of the pulmonary parenchyma is 1003 Hu. The pulmonary pattern is enhanced, the roots of the lungs are not enlarged, and the bronchi are traceable to the subsegmental level. Linear accumulations of air (McLean's effect) are detected in the perivascular and peribronchial connective tissue, located mainly in the root zone. The pleura is unchanged, there are no signs of fluid accumulation in the pleural cavity. The lung fields are symmetrical, with inflammatory infiltration of the lung tissue measuring 27*17 mm in S4 of the right lung.

When conducting an external respiration test (FER) with a bronchodilation test (salbutamol 200 mg), the following results were obtained: initial FEV_1— 73%, FVC_1 — 84% of the expected values, bronchodilation test positive (+18%) according to FEV_1).

Severe obstructive impairment of lung ventilation capacity.

Electrocardiography (ECG): rhythm with a heart rate of 122–130 beats per minute, vertical position of the electrical axis of the heart. To clarify the possible etiological nature of community-acquired pneumonia, the patient underwent molecular diagnostics using PCR of the nasopharyngeal and oropharyngeal mucosa: positive for *Mycoplasma pneumoniae*; *C. pneumoniae*, RS virus, parainfluenza virus types 1–4, metapneumoviruses, coronavirus, adenoviruses, bocavirus, rhinovirus — negative.

Bacteriological sputum culture for flora with determination of sensitivity to major antibiotics: *Streptococcus pneumoniae* growth obtained: $1*10^5$ CFU/ml. Sensitive to: amoxiclav (amoxicillin/clavulanic acid), norfloxacin, imipenem, cefepime, cefoxitin, ceftazidime, linezolid, erythromycin, clarithromycin.

ELISA blood test to detect antibodies to *Mycoplasma pneumoniae:* IgM detected, IgG not detected.

Based on the combination of epidemiological history, clinical and laboratory-instrumental data, the child was given a clinical diagnosis:

Primary: community-acquired segmental (S4) right-sided pneumonia, acute course, mild, complicated, RF I.

Concomitant: bronchial asthma, allergic form, moderate severity, moderate exacerbation, partially controlled course. Polyvalent sensitization (pollen, household, fungal).

Complications: spontaneous mediastinal emphysema (pneumomediastinum), subcutaneous emphysema. Based on the diagnosis and identified pathogens, the child was prescribed comprehensive therapy, including antibacterial, anti-inflammatory, bronchodilator, and symptomatic treatment. A combination of β-lactams and macrolides was used for antibacterial therapy: amoxicillin/clavulanic acid at a dose of 50 mg/kg/day (1 g twice a day) orally, azithromycin 500 mg/day orally for 5 days. Ibuprofen 200 mg 3 times a day was prescribed to relieve pain during coughing. Inhalation therapy with a 3% hypertonic solution twice a day was prescribed. Basic therapy was continued with the use of a combination drug — fluticasone propionate/salmeterol at a dose of 125/25 mcg, one dose twice a day, in the form of a metered dose inhaler.

Against the background of the treatment, positive dynamics in the patient's condition are noted. The patient has no complaints, and the clinical manifestations of intoxication and respiratory symptoms have disappeared. Palpation of the neck and chest reveals no subcutaneous emphysema. Body temperature is 36.8 °C, respiratory rate is 18 per minute, heart rate

is 102 beats per minute, blood pressure is 96/60 mm Hg, SpO2 is 98%. Laboratory tests (clinical and biochemical blood tests, urine tests) revealed no pathological abnormalities. Follow-up CT scans of the chest showed no signs of mediastinal, subcutaneous, or intermuscular emphysema. The total length of stay in the hospital was 12 days.

This clinical case illustrates the impact of *Mycoplasma pneumoniae* infection on the course of bronchial asthma in a child. The atypical pathogen exacerbated bronchial hyperreactivity and reduced the effectiveness of the immune response, leading to severe bronchial obstruction and deterioration of the patient's general condition. As a result of the complex combination of asthma and mycoplasma infection, the child developed a complication—spontaneous mediastinal emphysema. This case highlights the importance of timely diagnosis and a comprehensive approach to the treatment of infections in children with bronchial asthma in order to prevent the development of such complications. It is noteworthy that one of the most serious forms of respiratory mycoplasmosis, community-acquired pneumonia, was diagnosed in this family.

This case demonstrates the typical epidemiological characteristics of mycoplasma infection: seasonality (autumn-winter increase in incidence), slow spread and development of the disease with close family contact (within three weeks), and the patients' age.

DISCUSSION. This clinical case demonstrates the impact of *Mycoplasma pneumoniae* on the course of bronchial asthma in children and the development of complications, including spontaneous mediastinal emphysema. *Mycoplasma pneumoniae* is a common cause of atypical pneumonia in children and can contribute to the exacerbation of chronic respiratory diseases, including bronchial asthma. In this case, the infection led to the development of segmental pneumonia and severe bronchial hyperreactivity, which caused significant bronchial obstruction and deterioration of the general condition [10]. It is known that mycoplasma infection can induce hyperproduction of proinflammatory cytokines (IL-6, IL-8, TNF-α), which can exacerbate airway inflammation and reduce the effectiveness of basic asthma therapy [12].

Spontaneous mediastinal emphysema (pneumomediastinum) is a rare complication that occurs when intra-alveolar pressure increases, which can be observed against the background of intense coughing, severe bronchial obstruction, or enhanced lung ventilation [13]. The pathogenesis of this condition is explained by the Maclin effect: rupture of the alveoli followed by the spread of air through the perivascular and peribronchial spaces into the mediastinum. In this case, the development of emphysema was facilitated by severe bronchial obstruction against the background of an asthmatic process and mycoplasma pneumonia.

The diagnosis was based on a comprehensive examination, including molecular and serological methods for detecting *Mycoplasma pneumoniae*, as well as imaging methods (X-ray, chest CT scan). Hammann's sign, characteristic of spontaneous mediastinal emphysema, was of particular diagnostic significance. Computed tomography allowed for a detailed assessment of the extent of emphysema and ruled out other potential causes of mediastinal pathology. Treatment included antibiotic therapy with macrolides in combination with β-lactams, which ensured rapid elimination of the pathogen. An important aspect of treatment was the continuation of basic therapy for bronchial asthma, including inhaled corticosteroids and bronchodilators, which allowed for control of bronchial obstruction and reduced the risk of recurrence.

CONCLUSION. This clinical case demonstrates a complex combination of community-acquired mycoplasma pneumonia and bronchial asthma, complicated by the development of spontaneous mediastinal emphysema. The effect of the infection on the pathogenesis of asthma manifested itself in increased bronchial hyperreactivity, worsening disease control, and the development of severe bronchial obstruction. This case highlights the importance of timely detection of atypical respiratory infection pathogens in children with bronchial asthma and the need for a comprehensive approach to therapy, including antibacterial, anti-inflammatory, and bronchodilator treatment. In addition, the clinical case reflects the epidemiological features of mycoplasma infection: family clusters, a long incu-

bation period, and gradual development of the clinical picture. This emphasizes the need for epidemiological surveillance, timely diagnosis, and adequate antibiotic therapy to prevent complications, especially in patients with chronic respiratory diseases..

Further research into the impact of *Mycoplasma pneumoniae* on the course of bronchial asthma may contribute to the development of more effective strategies for the treatment and prevention of exacerbations in this patient group.

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FUNDING SOURCES

This study was not sponsored.

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ

Исследование проводилось без участия спонсоров.

THE AUTHORS' CONTRIBUTION TO THE WORK

Rezeda M. Fayzullina — conceptualization, formulation or evolution of overarching research goals and aims.

Anastasia E. Chernyshova — conceptualization, formal analysis, formal analysis, visualization, writing — review & editing.

Rita R. Gafurova — conceptualization, formal analysis, visualization, writing — review & editing.

Vladislav B. Golubyatnikov — conceptualization, formal analysis, investigation.

ВКЛАД АВТОРОВ В РАБОТУ

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CONSENT FOR PUBLICATION

Written voluntary informed consent has been obtained from the patient's parents to publish the description of the clinical case, as well as to use its clinical and medical data (examination results, observation and therapy) exclusively for scientific purposes.

ИНФОРМИРОВАННОЕ СОГЛАСИЕ НА ПУБЛИКАЦИЮ

От родителей пациента получено письменное добровольное информированное согласие на публикацию описания клинического случая, а также на использование его клинических и медицинских данных (результатов обследования, наблюдения и терапии) исключительно в научных целях.

Ассоциация детских аллергологов
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IN PEDIATRICS