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:

НОМЕР 1 (76) МАРТ 2024
ISSUE: 1 (76) MARCH 2024

Ассоциация детских аллергологов и иммунологов России
Наш подписной индекс: 47432

1 (76) 2024

ISSN 2712-7958 online | **Allergologiâ i immunologiâ v pediatrii** | **ISSN 2500-1175** print

ALLERGOLOGY AND IMMUNOLOGY IN PEDIATRICS

Volume 76 • Number 1 • March 2024

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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 magazine 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: March 20, 2024. The journal materials are distributed under a Creative Commons license.
The magazine 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 | Allergologiâ i immunologiâ v pediatrii | ISSN 2500-1175 print

АЛЛЕРГОЛОГИЯ И ИММУНОЛОГИЯ В ПЕДИАТРИИ

№ 1 (76), март 2024 г.

Журнал «Аллергология и иммунология в педиатрии» — рецензируемое научно-практическое периодическое издание, предназначенное для педиатров, аллергологов-иммунологов, а также специалистов разного профиля, работа которых связана с областью педиатрической аллергологии и иммунологии. Журнал является официальным печатным органом Ассоциации детских аллергологов и иммунологов России (АДАИР); издается при участии ведущих специалистов страны — педиатров, аллергологов, клинических иммунологов. На страницах издания — оригинальные статьи, образовательные программы для врачей, клинические наблюдения, дискуссии, информация о последних достижениях отечественной, зарубежной науки и практики. Все публикации журнала связаны с вопросами диагностики, лечения, профилактики аллергических и других иммуноопосредованных заболеваний у детей с акцентом на детскую аллергологию. Журнал основан в 2003 году. С 2003–2004 гг. носил название «Научно-практический журнал Аллергология и иммунология в педиатрии». В 2004 году переименован и носит название «Аллергология и иммунология в педиатрии».

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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

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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: 20.03.2024 г. Материалы журнала распространяются под лицензией Creative Commons.
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Подписной индекс издания 47432. Цена свободная.

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REV — обзорная статья

https://doi.org/10.53529/2500-1175-2024-1-5-11

Received 12.01.2024
The article is accepted for publication 15.02.2024

Conflict of Interest:
The authors state that there is no external funding for the study.
The authors declare a conflict of interest. The author is member of the editorial board of the journal: Dali Sh. Macharadze.

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Annotation
The increasing prevalence of atopic dermatitis (AD) over recent decades suggests that environmental factors play an important role in the etiology and pathogenesis of the disease. Nonspecific factors refer to external (or exposomal) factors and include human and natural factors that influence the health of a population: for example, the socioeconomic status of the patient; climate, including air temperature, exposure to ultraviolet radiation, air pollution; and living in a city or rural area. Although studies have shown the influence of these factors on the course of AD, in general, none of them significantly increases or decreases the risk of developing the disease. This review briefly discusses studies on the role of nonspecific environmental risk factors and their impact on the course of AD in children and adults.
Keywords: atopic dermatitis, nonspecific risk factors, climate, socio-economic conditions, urban/rural environment.

For citation: Macharadze DSh, Rassanova EA, Ruzhentsova TA, Galanina AV, Malyshev VS. Role of nonspecific risk factors in atopic dermatitis. Allergology and Immunology in Pediatrics. 2024; 1: 5-11. https://doi.org/10.53529/2500-1175-2024-1-5-11

Роль неспецифических факторов риска при атопическом дерматите

https://doi.org/10.53529/2500-1175-2024-1-5-11

Статья поступила 12.01.2024
Статья принята в печать 15.02.2024
УДК 616.5-002+616-053.2

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Авторы заявляют о конфликте интересов. Автор входит в редакционную коллегию журнала: Мачарадзе Д. Ш.

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Аннотация
Увеличение распространенности атопического дерматита (АтД) за последние десятилетия свидетельствует о том, что факторы окружающей среды играют важную роль в этиологии и патогенезе заболевания. Неспецифические факторы относятся к внешним (или экспосомным) факторам и включают человеческие и природные факторы, влияющие на здоровье популяции: например, социально-экономический статус больного; климат, в том числе температуру воздуха, воздействие ультрафиолетового излучения, загрязнение воздуха; а также проживание в городе или сельской местности. Несмотря на то, что в исследованиях показано влияние этих факторов на течение АтД, в целом ни один из них достоверно не увеличивает или не снижает риск развития заболевания. В этом обзоре кратко обсуждаются исследования, посвященные роли неспецифических внешних факторов риска и их влиянию на развитие и течение АтД у детей и взрослых.
Ключевые слова: атопический дерматит, неспецифические факторы риска, климат, социально-экономические условия, городская/сельская среда.

Для цитирования: Мачарадзе ДШ, Рассанова ЕА, Руженцова ТА, Галанина АВ, Малышев ВС. Роль неспецифических факторов риска при атопическом дерматите. *Аллергология и иммунология в педиатрии*. 2024; 1: 5-11. https://doi.org/ 10.53529/2500-1175-2024-1-5-11

The pathogenesis of atopic dermatitis (AtD) is affected by a number of environmental factors in different ways (i.e. exposomes) [1–3]. External (exposome) factors are divided into *nonspecific*, or *a general external environment*, (human and natural factors, affecting the health of the population, — climate, urban environment, social and economic conditions); *specific* (air humidity, ultraviolet (UV) radiation, allergens, microbes, diet, tobacco and other pollutants) and *internal environment*, *dependent on the host* (interaction between body cells, for example, cutaneous and intestinal microbiota; inflammation and oxidative stress) [2, 3].

According to the latest data, mechanisms, responsible for the onset and exacerbation of AtD, involve interactions between genes and epithelial barrier, immune disorders, skin dysbiosis as well as the effect of various environmental factors [4, 5]. Due to impaired skin barrier function, in particular due to a genetic defect (including filaggrin mutations), penetration of allergens and infectious agents into the skin becomes easier [6].

According to the new concept — *"hypothesis of epithelial barrier"* — inflammation in the epithelial layer, which covers the skin surface as well as respiratory, urogenital and gastrointestinal tract, develops, first of all, when patients live in the urban environment [1]. Epithelial cell activation and release of such cytokines as IL-33, IL-25, thymic stromal lymphopoietin(TSLP), etc., upon allergen exposure, infectious agents or tissue damage due to skin itching, cause immune responses of Th2-type [7, 8]. Although Th2 axis is considered major in AtD pathogenesis, recent studies confirm the involvement of additional immune pathways, in particular Th1, Th17 and Th22-lymphosites [7, 8].As a result of impaired epi-

thelial barrier function, due to external factors, there is also change in the microbiome structure; in conjunction with disorders of immune regulation, it affects the maintenance of chronic inflammation in the skin [2,4–6].

Any of exposome factors might cause exacerbation and trigger AtD. The most significant role of external factors (e.g., air pollution and climate) in children with variants of filaggrin mutation, having lesions on exposed skin (face, arms,neck) [6]. The famous American scientist Leung

D. believes that other equally important triggers with AtD are *S. aureus*, herpes simplex virus, stress and allergens [4].

Although the impact of various risk factors on AtD development has been shown in numerous studies and confirmed under experimental conditions, their role in the start of the atopic march has not been determined yet [7].

Meanwhile, a wide variety of risk factors with AtD has been studied mainly in children: starting from nutrition and ending with certain external and internal, in particular, in different periods (pre- and postnatal) child development [8].

In many cases patients use exposure to the specific triggers to control their disease activity. Among the many environmental factors that affect the course of AtD, some can even play a protective role (e.g., consumption of unpasteurized milk) [2, 3].

NONSPECIFIC FACTORS

Urbanization, air pollution and climate change are the global factors, which affect public health worldwide,in contrast to the local ones, one of which is, in particular, the healthcare system in in specific regions.

HEALTHCARE

Availability and quality of healthcare differ, depending on economic development of the country of residence, social status, race and ethnicity, including AtD patients [9]. It is clear that obstacles to obtaining highly qualified medical help are a lack of expert physicians and even medical institutions with a modern infrastructure [2]. Also, if a patient belongs to an economically poor family or lives in conditions with limited access to education, this directly affects the effectiveness of treatment, including the opportunity to purchase necessary medicine. Particularly, in patients with bronchial asthma the above-mentioned socio-economic conditions lead to an increase in exposure to allergens and the development of more frequent and severe attacks of the disease [10]. Also, dilapidated and old housing as well as living in ecologically unfavourable areas were associated with increased prevalence and a more severe course of AtD in children [9, 11]. On the other hand, a reduction in the risk of AtD in the children, living in rural areas was revealed in the population (black population of South Africa), homogeneous by ethnicity and geographical origin [12]. It has long been known that colonization of the skin *S. aureus* is as risk factor, with which researches associate severity of AtD, allergic sensitization and impaired barrier function of the epidermis [4–6].

It is interesting to note that even among children with bronchial asthma the highest indicators of positive skin culture on *S. aureus* were more common in those who lived in the city or families with a low income [13]. The level of air pollution, especially inside the premises is also associated with a patient's low socioeconomic status [14]. In turn, impediments to access to quality health care due to socioeconomic problems can contribute to the development of stress in patients [8].

URBAN/RURAL LIFESTYLE

Hygiene hypothesis has long been debated as a possible explanation for growing allergic diseases: in particular, it has been observed that the youngest child among brothers and sisters has the lowest risk of developing AtD; or this risk decreases in infants, visiting kindergarten in the first year of life [15].

Other evidence, supporting the importance of environmental factors with AtD,include ecological differences between a city and a village.

It is believed that AtD is more common among patients, living in the city, compared to rural and suburban areas [3]. However, according to meta-analysis, conducted in 2010 by Schram M. et al, out of 26 studies, included in the analysis, 11 show a significantly higher prevalence of AtD in patients, living in the city; 14 — no such association is found, and only 1 study identifies a lower incidence of AtD in patients, living in the city [16]. Thereby, this comparative analysis underlines the potential role of various environmental factors in developing AtD.

Although exact factors are not quite clear, one explanation is related to the effect of farm animals on human health. Moreover, a link is shown between certain elements of a rural way of life (especially, the consumption of unpasteurized milk) and a reduction in prevalence of AtD [17, 18]. There was an interesting study, conducted jointly by Finnish and Russian scientists in a population of children, living in a genetically homogenous, but economically different region of Karelia at the Russian-Finnish border [19]. The comparative analysis showed 3–10 times higher prevalence of allergic diseases (bronchial asthma, hay fever, AtD, rhinitis as well as atopic sensitization) in Finland than in Russian Karelia, and, moreover, these patterns persisted for 10 years of observation [19]. Skin microbiome and bacterial and fungal content in the nasal mucus are also contrastingly different with a predominance of the genus *Acinetobacter* in children, living in Russia.

In addition, the disruption of the gut microbiome, especially at an early age, might affect human immunity and atopy pathogenesis (development of tolerance or sensitization). The change of microbiocenosis in urban environments, taking antibiotics, reducing exposure to farm animals and(or) their absence lead to a low effect of endotoxins and increased Th2-cells in epithelial and mucous membranes in patients with allergic diseases [20].

The urban way of living is also associated with progression of AtD and atopic multimorbidity in children with atopy in their parents, filaggrin mutations and allergic polysensitization in the anamnesis [21].

CLIMATE

One of the reasons for rising prevalence of AtD in industrialized countries is considered global climate change: in particular, rise in air temperature and increased greenhouse gas emissions that cause changes in atmospheric UV radiation and air humidity [22]. Furthermore, climate changes (droughts; mass displacement of people from new uninhabitable areas, etc.) pose the greatest threat to health of people, living in low- and middle-income countries.

Climate factors (temperature and air humidity, precipitation, UV radiation, etc.) are characterized by severe seasonality, and all of them certainly affect the skin. Particularly, both local and global changes in the outside temperature might be associated with the severity of skin manifestations in patients with AtD (although we cannot exclude simultaneous relationship between these factor and others).

Meanwhile, evidence of the association between air temperature and prevalence of AtD contradicts each other, perhaps because of various analytical methods or criteria for determining cold or hot weather. Several studies showed that both high and low air temperature is associated with exacerbation of AtD in observed patients [23–28]. Thus, in the USA, where there is one of the most diverse climates in the world, the frequency of out-patient visits was the highest in adults and children with AtD, living in the east of the country, where there is the lowest temperature, which reached its peak in winter [23]. According to other data, only cold or, on the contrary, hot weather is associated with exacerbation of AtD [24, 25].

It is more logical to expect a decrease in the prevalence of AtD in areas with high air temperature [22, 24]. Usually people, living in warmer climates, spend more time outdoors, and, therefore, exposure to UV rays might have a protective effect on the skin [23]. On the other hand, patients with an established diagnosis of AtD do not tolerate high air temperature as heat can cause sweating. As a rule, with sweat, which may develop the irritation action on the skin and contribute to Th2-type inflammation, itching of the skin becomes worse. Children with AtD reacts most to changes in temperature, who have more severe symptoms in spring, autumn and winter [25].

Despite the fact that sun exposure has a positive effect on the skin (UV rays contribute to raising the level of antimicrobial peptides in the skin, modulate the composition of the microbiota, etc.), some studies have found an association between poorly con-

trolled AtD and higher air temperature, including children [26–28].

Patients with Atd do not also tolerate extreme cold weather that might cause dry and itchy skin. Low air temperature may contribute to production of Th2-cytokines and affect the activity of mast cells in the skin that is strongly correlated with inflammation and impaired epidermal barrier of the skin [29].

Two studies show a very significant impact of climate on the course of AtD. Thus, displacement of children aged 4–13 with severe AtD, living in Norway (subarctic/moderate climate), to the subtropical climate of Gran Canaria for 4 weeks led to a significant improvement in skin symptoms on SCORAD scale and quality of life as well as reduced need for local steroids in 1 and 3 months [30]. A rapid decline in the intensity of itching is also noted in adult patients with AtD, who underwent sanatorium treatment in the high mountain region of Davos, Switzerland [24].

It is important to consider the influence of other effects of climate change on AtD (cold and dry weather conditions, flood, etc.) [31, 32]. Scientists believe that global warming will be accompanied by flood due to melting polar ice, sea level rise and longer rains. Thus, during flood events, occurred in Thailand, there was a significant increase in emergency department visits of children aged 0–12, suffering from AtD [25].

Climate changes and global warming will probably contribute to an increase in the concentration of such aeroallergens as pollen and fungi in the air, and also in the duration of pollination of plants and allergenicity of pollen itself [30–33]. It is shown that higher air temperature is associated with the extension of flowering season, and higher levels of CO_2 contribute to an increase in biomass of pollen produced and its allergens. In particular, raising level of pollutants in the air causes changes in allergenicity of ambrosia pollen [33]. This, ultimately, exacerbates allergenic load in patients with seasonal rhinoconjunctivitis. The study by Krämer U. et al confirms deterioration of skin symptoms in children with AtD and sensitization to grass pollen in summer [30].

CONCLUSION

The impact of different exposome factors on the development and course of Atd has been found in many studies. However, according to the literature, there are the most studied issues related to specific exposome factors, including their exposure in the prenatal and early period of a child's life (type of feeding, exposure to air pollutants, in particular tobacco smoke, vitamin D level, contact with pets, etc.). Although studies show the effect of nonspecific exposome factors on clinical manifestations of AtD, generally, none of them reliably increase or, on the contrary, decrease the risk of disease in children.

Undoubtedly, other factors have a modulating effect on above-mentioned nonspecific ones. Particularly, viruses, allergens, antioxidants, different pollutants, etc., which are closely associated with environment. These and other questions require further study.

REFERENCES/ ЛИТЕРАТУРА

1. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol. 2021; 21 (11): 739–751. https://doi.org/10.1038/s41577-021-00538-7.
2. Sözener ZC, Cevhertas L, Nadeau K et al. Environmental factors in epithelial barrier dysfunction. J Allergy Clin Immunol. 2020; 145 (6): 1517–1528. https://doi.org/10.1016/j.jaci.2020.04.024.
3. Narla S, Silverberg JI. The Role of Environmental Exposures in Atopic Dermatitis. Curr Allergy Asthma Rep. 2020; 20 (12): 74. https://doi.org/10.1007/s11882-020-00971-z.
4. Leung D. Atopic dermatitis: age and race do matter! J Allergy Clin Immunol 2015; 136: 1265–1267. https://doi.org/10.1016/j.jaci.2015.09.011

5. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discov. 2022; 21 (1): 21–40. https://doi.org/10.1038/s41573-021-00266-6.
6. Carson C, Rasmussen M, Thyssen J et al. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. PLoSOne. 2012; 7: e48678. https://doi.org/10.1371/journal.pone.0048678.
7. Wegienka G, Zoratti E, Cole Johnson C. The role of the early-life environment in the development of allergic disease. Immunol Allergy Clin North Am 2015; 35: 1–17. https://doi.org/10.1016/j.iac.2014.09.002.
8. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol. 2017; 13 (1): 15–26. https://doi.org/10.1080/1744666X.2016.1212660.
9. Wan J, Oganisian A, Spieker A et al. Racial/Ethnic Variation in Use of Ambulatory and Emergency Care for Atopic Dermatitis among US Children. J Invest Dermatol. 2019; 139 (9): 1906–1913. https://doi.org/10.1016/j.jid.2019.02.024.
10. Kopel LS, Phipatanakul W, Gaffin J. Social disadvantage and asthma control in children. Paediatr Respir Rev. 2014; 15 (3): 256–262; quiz 262-3. https://doi.org/10.1016/j.prrv.2014.04.017.
11. McKenzie C, Silverberg JI. The prevalence and persistence of atopic dermatitis in urban United States children. Ann Allergy Asthma Immunol. 2019; 123 (2): 173–178. https://doi.org/10.1016/j.anai.2019.05.014.
12. Levin ME, Botha M, Basera W et al. Environmental factors associated with allergy in urban and rural children from the South African Food Allergy (SAFFA) cohort. J Allergy Clin Immunol. 2020; 145 (1): 415–426. https://doi.org/0.1016/j.jaci.2019.07.048.
13. Davis MF, Ludwig S, Brigham E et al. Effect of home exposure to Staphylococcus aureus on asthma in adolescents. J Allergy Clin immunol. 2018; 141 (1): 402–405. https://doi.org/10.1016/j.jaci.2017.06.031.
14. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. Allergy. 2020; 75 (1): 63–74. https://doi.org/10.1111/все.1394.
15. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol 2011; 41: 1–34. https://doi.org/10.1159/000323290.
16. Schram ME, Tedja AM, Spijker R. et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. Br J Dermatol. 2010; 162 (5): 964–973. https://doi.org/10.1111/j.1365-2133.2010.0968.
17. Burbank AJ, Sood AK, Kesic M et al. Environmental determinants of allergy and asthma in early life. J Allergy Clin Immunol. 2017; 140 (1): 1–12. https://doi.org/10.1016/j.jaci.2017.05.010.
18. Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? J Allergy Clin Immunol. 2006; 117 (6): 1374–1381. https://doi.org/10.1016/j.jaci.2006.03.008.
19. Ruokolainen L, Paalanen L, Karkman A. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. Clin Exp Allergy. 2017; 47 (5): 665–674. https://doi.org/10.1111/cea.12895.
20. Glatthardt T, van Tilburg Bernardes E, Arrieta M-C. The mycobiome in atopic diseases: Inducers and triggers. J Allergy Clin Immunol. 2023; 152: 1368–1375. https://doi.org/10.1016/j.jaci.2023.10.006.
21. Irvine A, Mina-Osorio P. Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide. Br J Dermatol. 2019; 181 (5): 895–906. https://doi.org/10.1111/bjd.17766.
22. Fleischer Jr AB. Atopic dermatitis: the relationship to temperature and seasonality in the United States. Int J Dermatol. 2019; 58: 465–471. https://doi.org/10.1111/ijd.14289.
23. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. J Invest Dermatol. 2013; 133 (7): 1752–1759. https://doi.org/10.1038/jid.2013.19.
24. Vocks E, Busch R, Fröhlich C et al. Influence of weather and climate on subjective symptom intensity in atopic eczema. Int J Biometeorol. 2001; 45 (1): 27–33. https://doi.org/10.1007/s004840000077.
25. Kim M, Kim YM, Lee J. Seasonal variation and monthly patterns of skin symptoms in Korean children with atopic eczema/dermatitis syndrome. Allergy and Asthma Proceedings. 2017; 38: 294–299. https://doi.org/10.2500/aap.2017.38.4055.
26. Kathuria P, Silverberg JI. Association of pollution and climate with atopic eczema in US children. Pediatr Allergy Immunol. 2016; 27 (5): 478–485. https://doi.org/10.1111/pai.12543.
27. Sargen MR, Hoffstad O, Margolis DJ. Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004–2012. J Invest Dermatol. 2014; 134 (1): 51–57. 10.1038/jid.2013.274.
28. Coates SJ, Enbiale W, Davis MDP, Andersen LK. The effects of climate change on human health in Africa, a dermatologic perspective: a report from the International Society of Dermatology Climate Change Committee. Int J Dermatol. 2020; 59 (3): 265–278. https://doi.org/10.1111/ijd.14759.
29. Maglie R, Souza Monteiro de Araujo D. et al. The role of TRPA1 in skin physiology and pathology. Int J Mol Sci. 2021; 22 (6): 3065. https://doi.org/10.3390/ijms22063065.

30. Krämer U, Weidinger S, Darsow U et al. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. J Invest Dermatol. 2005; 124 (3): 514–523. https://doi.org/10.1111/j.0022-202X.2005.23625.
31. Byremo G, Rød G, Carlsen KH. Effect of climatic change in children with atopic eczema. Allergy. 2006; 61 (12): 1403–1410. https://doi.org/10.1111/j.1398-9995.2006.01209.
32. Chen NT, Chen MJ, Wu CD, Guo YL. Emergency room visits for childhood atopic dermatitis are associated with floods? Sci Total Environ. 2021; 773: 145435. https://doi.org/10.1016/j.scitotenv.2021.145435.
33. El Kelish A, Zhao F, Heller W et al. Ragweed (Ambrosia artemisiifolia) pollen allergenicity: SuperSAGE transcriptomic analysis upon elevated CO2 and drought stress. BMC Plant Biol. 2014; 14: 176. https://doi.org/10.1186/1471-2229-14-176.

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Dali Sh. Macharadze — article design development, text writing, text editing.

Ekaterina A. Rassanova, Tatyana A. Ruzhentsova, Alena V. Galanina, Vladimir S. Malyshev —collection of literary data on the topic of the article.

ВКЛАД АВТОРОВ В РАБОТУ

Мачарадзе Д. Ш. — разработка дизайна статьи, написание текста, редактирование текста.

Рассанова Е. А., Руженцова Т. А., Галанина А. В., Малышев В. С. — сбор литературных данных по теме статьи.

The effect of vitamin D provision on biomarkers of inflammation in bronchial asthma in children

RAR — научная статья

https://doi.org/10.53529/2500-1175-2024-1-12-19

Received 08.11.2023
The article is accepted for publication 05.12.2023

Conflict of Interest:
The authors declare that they have no competing interests.
This study was not supported by any external sources of funding.

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Annotation

Introduction. Asthma is a widespread disease in childhood and has a persistent tendency to increase. Therefore, the search for factors influencing this process, as well as biomarkers reflecting the degree of asthma control, is an urgent problem.

Objective. To study the relationship of vitamin D levels with the serum periostin and TGF-β1 concentration in children with asthma.

Materials and methods. The cross-sectional (one-stage) study included 80 children aged 6 to 17 years (average age — 12±3.2 g). The subjects were divided into 2 groups: children with asthma — group 1 (n = 40); group 2 — the control group (n = 40). In all children, the assessment of the concentration of 25(OH)D, periostin and TGF-β1 in the blood serum was studied.

Results. Median (Me) 25(OH) in patients with asthma was statistically significantly lower than in children of the comparison group (16.7 ng/ml, versus 25.7 ng/ml, p = 0.017), and did not depend on the severity of the disease, corresponded to a deficiency condition in both mild (16.2 ng/ml) and with an average severity of asthma (16.8 ng/ml) (p = 0.041). Me of periostin in 1st group was within the normal range (730.2 ng/ml), but statistically significantly exceeded the indicator of 2nd group (539.7 ng/ml, $p < 0.05$) and did not depend on the age and duration of asthma. High rates of periostin were observed in children with moderate severity of asthma with a disease experience of 4–6 years (617.2 ng/ml). Me of TGF-β1 in both groups corresponded to normal values (309.0 and 369.6 pg/ml, respectively, $p > 0.05$) and did not depend on the age and duration of asthma.

Conclusions. VD deficiency is registered in children with asthma 2 times more often than in healthy children in Ryazan region. The serum concentration of periostin increased in proportion to the severity of asthma. Vitamin D deficiency can be one of the risk factors for the development of asthma and lead to an imbalance in the periostin and TGF-β system.

Keywords: asthma, vitamin D, periostin, transforming growth factor β1, children.

For citation: Belykh NA, Pisnyur IV, Nikiforov AA, Nikiforova LV. The effect of vitamin D provision on biomarkers of inflammation in bronchial asthma in children. *Allergology and Immunology in Pediatrics*. 2024; 1: 12-19. https://doi.org/10.53529/2500-1175-2024-1-12-19

Влияние обеспеченности организма витамином D на биомаркеры воспаления при бронхиальной астме у детей

https://doi.org/10.53529/2500-1175-2024-1-12-19

Статья поступила 08.11.2023
Статья принята в печать 15.12.2023
УДК 616.248-053.2-008.9:577.161.2

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

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Аннотация

Актуальность. Бронхиальная астма (БА) является широко распространенным в детском возрасте заболеванием и имеет стойкую тенденцию к росту. Поэтому поиск факторов, влияющих на этот процесс, а также биомаркеров, отражающих степень контроля БА, является актуальной проблемой.

Цель. Изучить взаимосвязь уровня витамина D с концентрацией периостина и TGF-β1 в сыворотке крови у детей с БА.

Материалы и методы. В поперечное (одномоментное) исследование были включены 80 детей в возрасте от 6 до 17 лет (средний возраст — 12±3,2 г.). Обследуемые были распределены на 2 группы: дети с БА — 1-я группа (n = 40); 2-я группа — контрольная группа (n = 40). У всех детей проводили оценку концентрации 25(OH)D, периостина и TGF-β1 в сыворотке крови.

Результаты. Медиана (Me) 25(OH)D витамина D у пациентов с БА была статистически значимо ниже, чем у детей группы сравнения (16,7 нг/мл, против 25,7 нг/мл, p = 0,017), и не зависела от тяжести течения заболевания, соответствовала дефицитному состоянию как при легкой степени (16,2 нг/мл), так и при средней степени тяжести БА (16,8 нг/мл) (p = 0,041). Me периостина в 1-й группе была в пределах нормы (730,2 нг/мл), но статистически значимо превышала показатель 2-й группы (539,7 нг/мл, p < 0,05) и не зависела от возраста и длительности БА. Высокие показатели периостина имели дети со средней степенью тяжести БА при длительности заболевания 4–6 лет (617,2 нг/мл). Me TGF-β1 в обеих группах соответствовала нормальным значениям (309,0 и 369,6 пг/мл соответственно, p > 0,05) и не зависела от возраста и длительности БА.

Заключение. В г. Рязани у детей с БА дефицит VD регистрируется в 2 раза чаще, чем у здоровых детей. Показатели периостина в сыворотке крови возрастали пропорционально степени тяжести БА. Дефицит витамина D может выступать одним из факторов риска развития БА и приводить к дисбалансу в системе периостина и TGF-β.

Ключевые слова: бронхиальная астма, витамин D, периостин, трансформирующего фактора роста β1, дети.

Для цитирования: Белых НА, Пизнюр ИВ, Никифоров АА, Никифорова ЛВ. Влияние обеспеченности организма витамином D на биомаркеры воспаления при бронхиальной астме у детей. *Аллергология и иммунология в педиатрии*. 2024; 1: 12-19. https://doi.org/10.53529/2500-1175-2024-1-12-19

INTRODUCTION

Bronchial asthma (BA) is one of the most common chronic diseases in children population and characterized by the presence of respiratory symptoms such as wheezing, shortness of breath, chest tightness, cough that are varied in time and intensity [1]. Internal (predominantly genetic) and external factors (allergens, tobacco smoke, industrial dust, atmospheric pollution) are involved in the development of asthma. The prevalence of BA increases from year to year and a rapid growth is particularly noted in children population that prompts a further search for factors, contributing to this trend as well as biomarkers, demonstrating the level of asthma control [2–4].

Periostin is one of markers of allergic inflammation, which is a protein of the epithelium extracellular matrix with a molecular weight of 90 kDa, belonging to the Fasciolide family. Periostin is expressed by osteoblasts, localized in fetal tissues, embryonic periosteum, placenta, heart valves, adrenal tissue, lungs and thyroid [5–6]. In BA the synthesis of periostin is carried out by fibroblasts, epithelial and endothelial cells as well as bronchial smooth muscle cells [7]. Periostin is involved in the acute phase of inflammation in BA, providing synthesis and secretion by eosino-

phils of IL-6 and IL- 8 interleukins, which transform β-1 and β-2 growth factors, cysteine leukotrienes and prostaglandin E2. Periostin forms congestion in the basement bronchial membrane in the chronic phase of inflammation, providing its thickening and remodeling. Periostin gene expression is under the control of numerous cytokines and hormones. Periostin expression regulators include bone morphogenetic proteins (type 2 and 4) platelet-derived growth factor, vascular endothelial growth factor, connective tissue growth factor-2, angiotensin II, IL-3, IL-4, IL-6 and IL-13. Literature data of recent years point out that patients with a higher concentration of periostin in the blood serum are characterized by a frequent persistence of bronchial inflammation, also higher probability of connective tissue restructuring of epithelium submucosal layer (remodeling) [8, 9].

In recent years, a special attention is paid to tissue growth factors in the study of processes of remodeling the respiratory tract in asthma. TGF-β1 is one of cytokines, involved in the process. Produced by epithelial cells of the bronchial mucosa, inflammatory infiltrate cells, TGF-β1 has a pronounced immunoregulatory, antiproliferative and regenerating effect. This cytokine correlates with increased activity of Th17, aggravating inflammation in the respiratory tract. Moreover, there are data, indicating the inhibitory effect of TGF-β1 on relaxation of smooth bronchial muscles by induction of shortening smooth muscle fibers and increasing bronchial hyperreactivity [10].

The role of vitamin D (VD) in the development and control of BA remains an active area of research. VD is a pleiotropic hormone, which, along with the regulation of calcium and phosphorus metabolism, has a strong immunomodulatory effect [11]. VD is able to inhibit the function of T-helpers type 2 (Th2-cells), and also the proliferation and differentiation of B-cells into plasma cells that causes a decrease in the secretion of immunoglobulins E (IgE) [12]. It is known that Th2-response plays a crucial role in all allergic diseases. Therefore, a growing interest in the impact of VD on the pathogenesis of chronic inflammation in BA is justified [13]. In БА VD, by affecting VD receptors (VDR), reduces hypertrophy of bronchial smooth muscles, hyperplasia of goblet cells, subepithelial collagen deposition and fibroblast activity that leads to a lower rate of remodeling process [14, 15].

Thus, study of the relationship between VD concentration and inflammation biomarkers in BA is a relevant objective.

OBJECTIVE OF THE STUDY

Study the relationship of vitamin D level with the serum periostin and TGF-β1 concentration in children with BA.

MATERIALS AND METHODS

One-stage single-site randomized study involved 80 children aged 6-17 (average age — 12 ± 3,2), including girls — 29 (36,0 %), boys — 51 (64,0 %), permanently residing in Ryazan. The children were divided into 2 groups: group 1 (main group) included 40 children with BA, group 2 contained 40 children (control group) (Table 1). The main group is divided into 2 subgroups: 1а — children with moderate asthma (n = 23, 57,5 %), 1б — children with a mild disease (n = 17, 42,5 %).

The study plan was approved by the local Ethics Committee, FSBEI HE RyazSMU of the Ministry of Health of Russia (Protocol of 09.03.2021). The parents of all the children, taking part in the study,

Table 1. **Characteristics of the study participants**
Таблица 1. **Характеристика участников исследования**

Indocator	Group 1 (n = 40)	Group 2 (n = 40)	p
Age, years	12,0±2,8	11,9±3,3	0,96
Girls, n (%)	15 (37,5 %)	14 (35,0 %)	0,12
Boys, n (%)	25 (62,5 %)	26 (65,0 %)	0,20

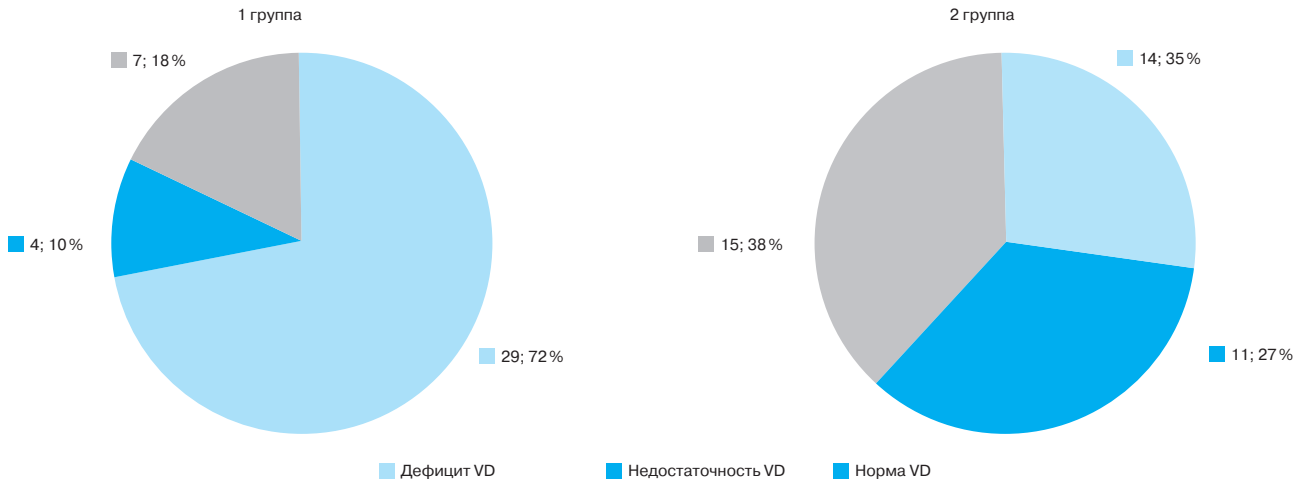

Fig. 1. **Provision of the examined children with VD**
Рис. 1. **Обеспеченность обследованных детей VD**

were familiarized with the regulation of the study and signed an informed consent.

SBI "City children's clinic № 3» (chief medical officer — A. O. Burdukova), Central research laboratory of FSBEI HE RyazSMU of the Ministry of Health of Russia (the head of the laboratory — candidate of medical science, associate professor A. A. Nikiforov) were bases to conduct the study.

Criteria for inclusion in the study: the established diagnosis of "bronchial asthma" for at least 1 year, verified according to GINA2022 [16] and Federal clinical guidelines [1]; patient age of 5-17 years; obtaining informed consent from parents and patients for the study.

Exclusion criteria: the presence of malignant neoplasm in the surveyed, an acute disease or exacerbation of other chronic diseases, endocrine or genetic pathology, surgery for the past 4 weeks, intake of anti-spasmatic drugs, disorders of calcium-phosphorus metabolism.

Material sampling was in March-April, 2021. Serum concentration 25(OH) D, periostin, TGF-β1 were determined by the ELISA method, using "25OH Vitamin D Total ELISA Kit" (DIAsourceImmunoAssaysSA, Belgium),

«ELISA Kit for Periostin», (Cloud-Clone Corp., USA), "ELISA Kit for Transforming Growth Factor Beta 1" (Cloud-Clone Corp., USA) in the Central Research laboratory, FSBEI HE RyazSMU of the Ministry of Health of Russia with further calculation of the median and interquartile range (Me; 25–75%). The obtained results were evaluated according to the National Program "Vitamin D insufficiency in children and adolescents in the Russian Federation: modern approaches to correction" (2018). Concentration 25(OH)D > 30 ng/mL was considered as the normal level, moderate deficiency — 21–30 ng/ml, severe deficiency — < 20 ng/ml [17]. Periostin value in the serum samples/plasma in 500-fold dilution: 132,4~859,6 ng/ml. TGF-β1 value in 3-fold dilution in the serum/plasma: 82,4~702,4 pg/ml [18].

Statistical data processing was conducted using MS Excel 2016 and Statistica 6.0 standard software packages. Shapiro-Wilk tests were used to analyze the normality of parameter distribution. Continuous variable was presented as the median (Me) with interquartile range (25–75 percentile). Categorial variables were determined in as a percentage (%). The assessment of differences between groups was conducted using non-parametric Mann-Whitney (U-test) and Pearson's (χ^2) tests with corrections for small samples. Differences were considered significant at $p < 0,05$.

STUDY RESULTS AND THEIR DISCUSSION

The examination revealed that most children had low level of 25(OH)D in the blood serum. At the same time, VD deficiency was recorded twice as often as in the control group ($p = 0,002$) (fig. 1).

The median of 25(OH)D in the group of children with BA was 1,5 times as low as in the control group and corresponded to the deficient condition — 16,7 ng/ml [7,1; 22,8] versus 25,7 ng/ml [17,4; 34,2] in group 2, respectively (p = 0,017).

The severity of the disease in children did not depend on the concentration of 25(OH)D in the blood serum in the main study group. Me in children with mild BA was 16,2 ng/ml [13,5; 22,8]), versus 16,8 ng/ml [13,9; 21,6] in the moderate severity (p = 0,041). 11,7 % (n = 2) of children with mild and 21,7 % (n = 5) with moderate asthma had optimal VD vitamin sufficiency. 37,5 % (n = 15) of children of the control group had normal VD-status.

Me 25(OH)D did not reach optimal values in any age category of children with BA, however, the rate in group 1 with teenage children was statistically significantly lower than in the control group (p < 0,05) (Table 2).

Periostin median in the group of children with BA was statistically much higher than the rate of the control group — 730,0 ng/ml [390,8; 1109,7] versus 536,7 ng/ml [452,0; 666,2] in group 2, respectively (p = 0,044) (fig. 2).

In the group of children with BA 30,0 % (n = 12) had the increased level of periostin. Periostin Me was 593,0 ng/ml [318,0; 846,3] with mild BA versus 751,0 ng/ml [505,0; 1140,0] with moderate BA (p = 0,027). 23,5 % (n = 4) of children with mild and 34,7 % (n = 8) with moderate asthma experienced the increased level of periostin (p > 0,05). 15,0 % (n = 6) of children in the control group had the same increased level. This is probably due to the activity of bone metabolism during active growth.

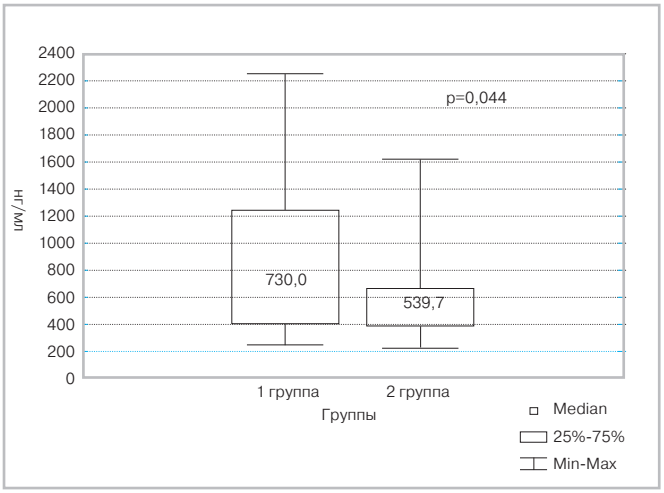

Fig. 2. **Median periostin in the blood serum of the examined children (ng/ml)**
Рис. 2. **Медиана периостина в сыворотке крови у обследованных детей (нг/мл)**

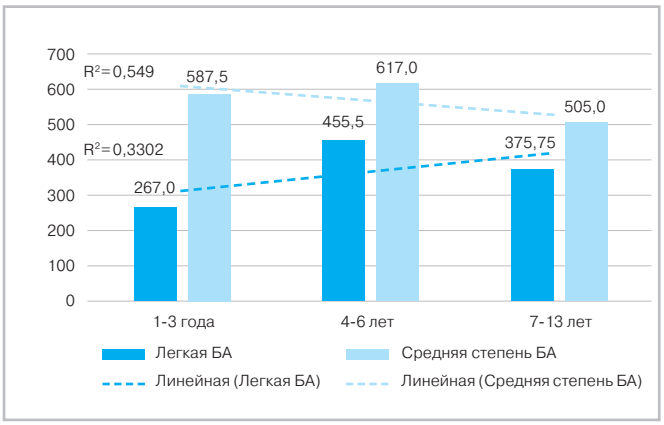

Fig. 3. **Median periostin in blood serum in children with asthma depending on the duration of the disease (ng/ml)**
Рис. 3. **Медиана периостина в сыворотке крови у детей с БА в зависимости от длительности заболевания (нг/мл)**

Table 2. **Median 25(OH)D in the blood serum of the examined children (ng/ml)**
Таблица 2. **Медиана 25(OH)D в сыворотке крови у обследованных детей (нг/мл)**

Age, years (n)	Group 1 Me [25 %; 75 %]	Group 2 Me [25 %; 75 %]	p
5–6 years (n = 3)	16,8 [16,8; 16,8]	32,7 [25,0; 40,4]	>0,05
7–9 years (n = 19)	19,4 [15,7; 30,5]	31,1 [21,1; 40,1]	>0,05
10–14 years (n = 36)	16,7 [13,7; 21,9]	25,3 [17,7; 33,5]	>0,05
15–17 years (n = 22)	13,5 [11,7; 16,9]	24,4 [16,6; 26,8]	<0,05

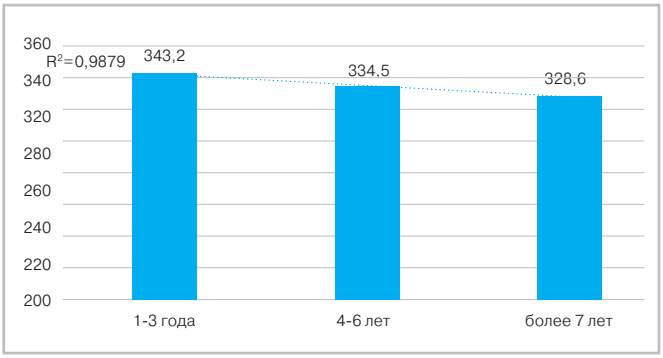

Fig. 4. **Median TGF-β1 in blood serum in children depending on the duration of AD (pg/ml) (p > 0.05)**
Рис. 4. **Медиана TGF-β1 в сыворотке крови у детей в зависимости от длительности БА (пг/мл) (p > 0,05)**

Me of periostin did not depend on the duration of the disease among children with BA, but this rate was higher (p >0,05) with moderate BA (fig. 3).

No clear correlation was found in the analysis of the relationship between the level of periostin and VD (Table 3).

The median of TGF-β1 in both groups of the examined children corresponded to normal values: 309,0 pg/ml [210,9; 408,6] and 355,0 pg/ml [257,4; 426,8], respectively (p > 0,05). However, Me TGF-β1 was statistically significantly lower among children with mild BA than in moderate asthma (300,9 [154,5; 342] pg/ml), versus 369,6 [296,1; 455,7] mg/ml, respectively, and lower than in children of the control group (355,0 pg/ml [257,4; 426,8]) (p < 0,05).

Me TGF-β1 in the blood serum was within the normal values in children with BA, and the lowest rate was noted with the duration of BA more than 7 years, which may indicate the properly selected anti-inflammatory therapy and high patient compliance (p > 0,05) (fig. 4).

Published meta-analysis of recent literature review indicate the presence of low VD sufficiency among pediatric patients with BA. The works by Wang Q et al. (2021) note that the level of 25(OH)D in the blood serum was much lower in children with BA (5 711 participants) than in children without asthma (21 561 people) [19]. The same results were obtained by Russian researchers (S. S. Masalskiy et al., 2018) [20]. The findings coincide with the conclusions of these authors — low VD sufficiency was detected in more than 70% of the examined children with BA.

The relationship between the level of periostin in the blood serum and the presence of BA is also being actively discussed. Inoue T. et al. (2016) noted that the concentration of periostin in the blood serum was higher in children with BA, compared to children with no allergic diseases. The authors also pointed to the need for determining periostin content in the blood serum to diagnose and monitor BA in children [21]. The works by Song J. S. et al. (2015) found that a high level of periostin in the blood serum in children with BA was associated with hyperreactivity of the respiratory tract [22, 23] S. S. Masalskiy and others. (2018) revealed that the level of serum periostin was significantly higher in children with BA, compared to healthy children, and directly correlated with the severity of BA [24]. In our study the level of periostin in the blood serum in children with BA was also statistically much higher than the rate of children in the control group, though, these figures were within the normal values and the concentration of periostin

Table 3. **Distribution of children by level 25(OH)D and periostin in blood serum in children with asthma**
Таблица 3. **Распределение детей по уровню 25(OH)D и периостина в сыворотке крови у детей с БА**

Rate	Increase in the concentration of periostin in the blood serum, n (%)	Normal concentration of periostin in the blood serum, n (%)	p
Severe VD deficiency, (n = 29)	10 (34,5 %)	19 (65,5 %)	> 0,05
Moderate VD deficiency, (n = 4)	1 (25,0 %)	3 (75,0 %)	> 0,05
Norm of VD, (n = 7)	1 (14,3 %)	6 (85,7 %)	> 0,05

in children with moderate BA was statistically significantly higher than in a mild degree of the disease, though both the rates were within the normal values.

It is considered that TGF-β1 plays a central role in the pathogenesis of remodeling the respiratory tract in BA, which can occur at any age, regardless of the severity degree and is caused by complex pathogenetic interactions between different biologically active molecules and external triggers. The work by N. L. Potapova, I. N. Gaymolenko (2019) revealed a significant difference in the content of serum TGF-β1 in children with BA, compared to the group of healthy children [10]. Our study has not found incidents of the increased content of serum TGF-β1 in either patients with BA or the controlled group. In this case, patients with mild BA had the level of TGF-β1 statistically much lower than in the moderate severity of the disease.

CONCLUSIONS:

1. The incidence of vitamin D deficiency in children with BA from Ryazan was recorded twice as often as in healthy children, and it did not depend on the severity of asthma.
2. Periostin rate in the blood serum increased in proportion to the severity of BA.
3. Vitamin D deficiency may be one of risk factors for developing BA, causing imbalance in the system of periostin and TGF-β.
4. It is advisable to monitor the level of 25(OH) D in the blood serum with subsequent correction in children with BA.

REFERENCES/ЛИТЕРАТУРА

1. Бронхиальная астма: федеральные клинические рекомендации по диагностике и лечению. 2021. 118 с. [Bronchial asthma: federal clinical guidelines for diagnosis and treatment. 2021. 118 p. (In Russ.)]
2. Белых НА, Пизнюр ИВ. Современные представления о роли витамина Д в патогенезе бронхиальной астмы у детей. Наука молодых (Eruditio Juvenium). 2020; 8 (4): 617–628. [Belykh NA, Pisnyur IV. Modern ideas about the role of vitamin D in the pathogenesis of bronchial asthma in children. The Science of the Young (Eruditio Juvenium). 2020; 8 (4): 617–628. (In Russ.)] https://doi.org/10.23888/HMJ202084617-628.6.
3. Трибунцева ЛВ, Авдеев СН, Будневский АВ, Прозорова ГГ, Кожевникова СА. Сочетанное влияние мультиморбидности и повышенного индекса массы тела на контроль бронхиальной астмы и качество жизни пациентов. Российский медико-биологический вестник им. академика И. П. Павлова. 2023; 31 (1): 37–48. https://doi.org/10.17816/PAVLOVJ111895. [Tribuntseva LV, Avdeev SN, Budnevsky AV, Prozorova GG, Kozhevnikova SA. The combined effect of multimorbidity and an increased body mass index on the control of bronchial asthma and the quality of life of patients. academician I. P. Pavlov. 2023; 31 (1): 37–48. https://doi.org/10.17816/PAVLOVJ111895. (In Russ.)]
4. Salmanpour F, Kian N, Samieefar N, et al. Asthma and Vitamin D Deficiency: Occurrence, Immune Mechanisms, and New Perspectives. IJ Immunol Res. 2022; 2022: 1–7. https://doi.org/10.1155/2022/6735900.
5. Izuhara K, Nunomura S, Nanri Y, et al. Periostin: An emerging biomarker for allergic diseases. Allergy. 2019; 74 (11): 2116–2128. https://doi.org/10.1111/all.13814.
6. Novosad J, Krčmová I, Bartoš V, et al. Serum periostin levels in asthma patients in relation to omalizumab therapy and presence of chronic rhinosinusitis with nasal polyps. Postepy Dermatol Alergol. 2020; 37 (2): 240–249. https://doi.org/10.5114/ada.2020.94842.
7. Yu L, Wang J, Liu K. Role of periostin in ECRS. Eur Arch Otorhinolaryngol. 2021; 278 (8): 2665–2672. https://doi.org/10.1007/s00405-020-06369-x.
8. Turczyn A, Pańczyk-Tomaszewska M. The role of periostin in kidney diseases. Cent Eur J Immunol. 2021; 46 (4): 494–501. https://doi.org/10.5114/ceji.2021.110317.2021.
9. Alzobaidi N, Rehman S, Naqvi M, Gulati K, Ray A. Periostin: A Potential Biomarker and Therapeutic Target in Pulmonary Diseases. J Pharm Pharm Sci. 2022; 25: 137–148. https://doi.org/10.18433/jpps32306.
10. Потапова НЛ, Гаймоленко ИН. Анализ уровня трансформирующего фактора роста В1 у детей, больных бронхиальной астмой. Мать и дитя в Кузбассе. 2019; 4 (79): 21–25. [Potapova NL, Gaimolenko IN. Analysis of the level of transforming growth factor B1 in children with bronchial asthma. Mother and child in Kuzbass. 2019; 4 (79): 21–25. (In Russ.)].
11. Rozmus D, Ciesielska A, Płomiński J, et al. Vitamin D Binding Protein (VDBP) and Its Gene Polymorphisms-The Risk of Malignant Tumors and Other Diseases. Int J Mol Sci. 2020; 21 (21): 7822 https://doi.org/10.3390/ijms21217822.
12. Li Q, Zhou Q, Zhang G. et al. Vitamin D Supplementation and Allergic Diseases during Childhood: A Systematic Review and Meta-Analysis. Nutrients. 2022; 14 (19): 3947. https://doi.org/10.3390/nu14193947.

13. Williamson A, Martineau AR, Sheikh A, et al. Vitamin D for the management of asthma. Cochrane Database Syst Rev. 2023; 6 (2): CD011511. https://doi.org/10.1002/14651858.CD011511.pub3.
14. Esfandiar N, Alaei F, Fallah S, et al. Vitamin D deficiency and its impact on asthma severity in asthmatic children. Ital J Pediatr. 2016; 42 (1): 108. https://doi.org/10.1186/s13052-016-0300-5.
15. Costa Dias Ladeira JM, Zacas O, Ferreira AM. et al. The role of vitamin D in the severity and control of asthma in children and adolescents: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2022; 101 (50): e31457. https://doi.org/10.1097/MD.0000000000031457.
16. Global Strategy for Asthma Management and Prevention. Updated 2022. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf
17. Боровик ТЕ, Громова ОА, Захарова ВВ, Мальцев СВ, Мошетова ЛК, Намазова-Баранова ЛС и др. Недостаточность витамина D у детей и подростков Российской Федерации: современные подходы к коррекции. Национальная программа. Москва. Издательский дом «Педиатр», 2021. 116 с. [Borovik TE, Gromova OA, Zakharova VV, Maltsev SV, Moshetova LK, Namazova-Baranova LS, etc. Vitamin D deficiency in children and adolescents of the Russian Federation: modern approaches to correction. The national program. Moscow. Publishing house «Pediatrician», 2021. 116 p. (In Russ.)]
18. Калашникова ЛА, Данилова МС, Шабалина АА. и др. Трансформирующий фактор роста бета у больных с диссекцией внутренних сонных и позвоночных артерий. Журнал неврологии и психиатрии им. С. С. Корсакова 2022; 122 (10): 82–87. [Kalashnikova LA, Danilova MS, Shabalina AA et al. Transforming growth factor beta in patients with dissection of internal carotid and vertebral arteries. Journal of Neurology and Psychiatry named after S. S. Korsakov. 2022; 122 (10): 82–87. (In Russ.)] https://doi.org/10.17116/jnevro202212210182.
19. Wang Q, Ying Q, Zhu W, et al. Vitamin D and asthma occurrence in children: A systematic review and meta-analysis. J Pediatr Nurs. 2022; e60–e68. https://doi.org/10.1016/j.pedn.2021.07.005.
20. Масальский СС, Калмыкова АС, Уханова ОП. Особенности обеспеченности витамином D при различном клиническом течении бронхиальной астмы у детей и подростков. Аллергология и иммунология в педиатрии. 2018; 1 (52): 25–32. [Masalskiy SS, Kalmykova AS, Ukhanova OP. Features of vitamin D provision in various clinical course of bronchial asthma in children and adolescents. Allergology and immunology in pediatrics. 2018; 1 (52): 25–32. (In Russ.)]
21. Inoue T, Akashi K, Watanabe M, et al. Periostin as a biomarker for the diagnosis of pediatric asthma. Pediatr Allergy Immunol. 2016; 27 (5): 521–526. https://doi.org/10.1111/pai.12575.
22. Song JS, You JS, Jeong SI, et al. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. Allergy. 2015; 70 (6): 674–681. https://doi.org/10.1111/all.12599.
23. Yavuz ST, Bagci S, Bolat A, et al. Association of serum periostin levels with clinical features in children with asthma. Pediatr Allergy Immunol. 2021; 32 (5): 937–944. https://doi.org/10.1111/pai.13444.
24. Масальский СС, Калмыкова АС, Уханова ОП. Комплексная оценка сывороточного периостина — нового маркера аллергического воспаления при неконтролируемой БА у детей. Российский Аллергологический Журнал. 2018; 15 (1S): 55–57. https://doi: 10.36691/RJA49. [Masalskiy SS, Kalmykova AS, Ukhanova OP. Complex evaluation of serum periostin — new marker of allergic inflammation at uncontrolled bronchial asthma at children. Russian Journal of Allergy. 2018; 15 (1S): 55–57. https://doi.org/10.36691/RJA49. (In Russ.)]

THE AUTHORS' CONTRIBUTION TO THE WORK

Natalia A. Belykh – development of the concept and design of the study, editing the text of the article.

Inna V. Pisnyur – review of publications on the topic of the article, collection of material, statistical data processing, text preparation, writing and editing of the text of the article.

Aleksandr A. Nikiforov, Larisa V. Nikiforova – conducting research, analyzing the data obtained.

ВКЛАД АВТОРОВ В РАБОТУ

Белых Н. А. — разработка концепции и дизайна исследования, редактирование текста статьи.

Пизнюр И. В. — обзор публикаций по теме статьи, сбор материала, статистическая обработка данных, подготовка текста, написание и редактирование текста статьи.

Никифоров А. А., Никифорова Л. В. — проведение исследования, анализ полученных данных.

A clinical case of atopic dermatitis with a rapid positive effect from the use of a genetically engineered biological drug in a teenager

RAR — научная статья

https://doi.org/10.53529/2500-1175-2024-1-20-26

Received 10.11.2023
The article is accepted for publication 01.03.2024

Conflict of Interest:
The authors state that there is no external funding for the study.
The authors declare a conflict of interest. The author is member of the editorial board of the journal: Ella V. Churyukina.

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Annotation

Introduction. The instructions for the drug dupilumab indicate that the administration of a single loading dose on the first day leads to the rapid achievement of clinically effective concentrations within 2 weeks, which we saw in the example of our patient and her real clinical response to the first injection.

Presentation of a clinical case. Under our medical supervision was a 17-year-old patient with severe atopic dermatitis, resistant to traditional therapy. Heredity for allergic pathology is burdened: the girl's mother suffers from pollen allergy. Initially before the start of therapy: SCORAD — 88 points, EASI — 48.8 points, IGA — 4, blood eosinophils — 11% (1188 cells/ml), total IgE — 1102.0 IU/ml; the content of nitric oxide in exhaled air (FeNO) is 30 ppb. On April 28, 2021, the patient was administered dupilumab at a dose of 600 mg. Assessment of atopic dermatitis control in points upon admission to the hospital 2 weeks after the first administration of dupilumab: on the SCORAD scale — 44.5 points; EASI — 13.8 points; IGA — 2 points, eosinophils — 9% (1070 cells/ml); total IgE — 840 IU/ml; FeNO — 5 ppb.

Conclusion. This clinical observation clearly illustrates the fact that patients with severe atopic dermatitis who don't respond to first-line therapy can achieve positive clinical results after the first use of a recombinant human monoclonal antibody (IgG4).

Keywords: atopic dermatitis, biotherapy, dupilumab.

For citation: Churyukina EV, Portnyaga EA. A clinical case of atopic dermatitis with a rapid positive effect from the use of a genetically engineered biological drug in a teenager. *Allergology and Immunology in Pediatrics*. 2024; 1: 20-26. https://doi.org/10.53529/2500-1175-2024-1-20-26

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Клинический случай атопического дерматита с быстрым положительным эффектом от применения генно-инженерного биологического препарата у подростка

https://doi.org/10.53529/2500-1175-2024-1-20-26

Статья поступила 10.11.2023
Статья принята в печать 01.03.2024
УДК: 615.036.8

Конфликт интересов:
Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Авторы заявляют о конфликте интересов. Автор входит в редакционную коллегию журнала: Чурюкина Э. В.

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Аннотация

Введение. В инструкции к препарату дупилумаб указано, что введение однократной нагрузочной дозы в первый день приводит к быстрому достижению клинически эффективных концентраций в течение 2 недель, что мы и увидели на примере нашей пациентки и ее реального клинического ответа на введение уже первой инъекции.

Изложение клинического случая. Под нашим медицинским наблюдением находилась пациентка 17 лет с тяжелым течением атопического дерматита, резистентного к традиционной терапии. Наследственность по аллергической патологии отягощена: мать девочки страдает пыльцевой аллергией. Исходно до начала терапии: SCORAD — 88 баллов, EASI — 48,8 балла, IGA — 4, эозинофилы крови — 11% (1188 кл/мл), общий IgE — 1102,0 МЕ/мл; содержание оксида азота в выдыхаемом воздухе (FeNO) — 30 ppb. 28.04.2021 больной введен дупилумаб в дозе 600 мг. Оценка контроля атопического дерматита в баллах при поступлении в стационар через 2 недели после первого введения дупилумаба: по шкале SCORAD — 44,5 балла; EASI — 13,8 балла; IGA — 2 балла, эозинофилы — 9% (1070 клеток/мл); общий IgE — 840 МЕ/мл; FeNO — 5 ppb.

Заключение. Данное клиническое наблюдение наглядно иллюстрирует тот факт, что пациенты с тяжелой степенью атопического дерматита, не отвечающие положительным эффектом на первые линии терапии, могут достичь положительных клинических результатов уже после первого применения рекомбинантного человеческого моноклонального антитела (IgG4).

Ключевые слова: атопический дерматит, биотерапия, дупилумаб.

Для цитирования: Чурюкина ЭВ, Портняга ЕА. Клинический случай атопического дерматита с быстрым положительным эффектом от применения генно-инженерного биологического препарата у подростка. *Аллергология и иммунология в педиатрии*. 2024; 1: 20-26. https://doi.org/10.53529/2500-1175-2024-1-20-26

INTRODUCTION

Atopic dermatitis is a multifactorial genetically determined inflammatory skin disease, characterized by itching, chronic recurrent course, age characteristics of localization and morphology of lesions [1]. To date, there is a constant growth of atopic diseases in the world, which earliest from of manifestation is exactly atopic dermatitis that develops against the backdrop of genetic predisposition to atopy [2].

Modern understanding of AtD pathogenesis is based on immunological peculiarities of lymphocytic infiltrate with an admixture of dendritic cells, an increased level of inflammatory mediators in the affected tissues and defects in the skin barrier [3]. It was revealed that the basis of allergic disease is the change in the correlation of subpopulations of T-helper cells in favor of TH2 phenotype [2]. It is T2-inflammation that the basis of a range of diseases, such as bronchial asthma, allergic rhinitis, chronic polypous rhinosinusitis, atopic dermatitis, eosinophilic esophagitis, etc. [4]. Il-4, Il-13 and IL-5 are key cytokines, involved in a cascade of inflammatory responses in T2-inflammation. It is worth noting that a combination of allergic diseases is common in clinical practice: bronchial asthma (BA), allergic rhinitis and AtD [4, 5]. Considering the contribution of the same cytokines to the

development of inflammation in various conditions, it might seem perspective to use one drug for treating various T2-associated diseases in one patient [4, 6].

The appeared information on the pathogenesis of AtD development prompted scientists to search for drugs, inhibiting cytokines, involved in the process of inflammation. Modern immunology is actively studying the role of particular cells and molecules in the pathogenesis of allergic diseases for diagnosing, treating and monitoring the efficiency of therapy [7]. Dupilumab has become the first targeted biological drug to treat AtD. It is a recombinant monoclonal antibody to IL-4 and IL-13 receptor subunit, which suppresses T2-inflammatory response through inhibition of two key cytokines and might be the preferred drug for treating moderate and severe continuously recurrent AtD [8]. Dupilumab is responsible for inhibiting immune disorders, characterized by Th2 phenotype [9, 10]. Clinical trial, conducted for more than 10 years, has confirmed the efficiency and safety of dupilumab for treating AtD [11–13]. A large number of studies demonstrate the efficacy of dupilumab to treat all cases, characterized by Th2-mediated inflammation [4, 14]. In Russia dupilumab is approved for administration in the treatment of patients aged 6 and over for indications "moderate and severe AtD", under the age 12 years — "bronchial asthma", under the age of 18 years — "polypous rhinosinusitis" [15]. The drug is available in the prefilled syringe, containing 200 or 300 mg of dupilumab. Dupilumab is administered and can be stored at room temperature (до 25 °C) within 14 days if necessary; injection can be done by either the patient (in the hip or abdomen area) or the caregiver (in the upper arm) [4, 16].

DESCRIPTION OF THE CLINICAL CASE

A girl (17 years), burdened by heredity for allergic pathology (the girl's mother suffers from pollen allergy), has been afflicted with atopic dermatitis from an early age. Skin syndrome debuted from 6 months in the form of hyperemia in the upper extremities. The pediatrician diagnosed "sweating fever". At the age of 10 months hyperemia occurred in the upper and lower extremities, the allergist diagnosed "atopic dermatitis, food allergy". Treatment was prescribed with methylprednisolone aceponate with a positive effect.

Skin syndrome relapsed up to 5 years in spring and autumn with the improvement in summer while being at sea. She was hospitalized due to developed streptoderma at the age of 3.

In 2013 she contacted a dermatovenerologist at the place of residence with a severe exacerbation. Local therapy was prescribed. A temporary positive effect was observed for 1–2 months.

The disease had wave-like nature, topical glucocorticosteroid (GCS) drugs were used with a short-term positive effect in courses for 5 years.

Since January, 2020 there has been a pronounced deterioration after stress from the words of the patient. In the spring 2020 she was hospitalized to the regional hospital at the place of residence with complaints of flushing of the skin, itching, scratching, lichenization in the upper and lower extremities, back and face; she got intravenous administration of dexamethasone (4 mg), 0,9 % solution of sodium chloride, antihistamines, external therapy with GCS with no positive effect.

Due to refractoriness to the therapy, she has repeatedly received inpatient treatment since March, 2020. There was constant intake of non-sedating antihistamines and topical glucocorticosteroids; systemic antihistamines in the hospital.

Allergy testing (21.04.2020) (S-IgE): pollen (meadow grass — 2 class); household (house dust— 3 class); epidermal (cat hair — 3 class, dog hair — 2 class); food (chicken eggs — 3 class).

There are no cats and dogs in the patient's house, no chicken eggs consumed and regular wet cleaning.

In December, 2020, due to persistent rash, the patient went to the hospital at the new place of residence, where she got therapy with no positive effect. She received standard care in FSBI "State Scientific Centre of Dermatovenereology and Cosmetology", the Ministry of Health of Russia in conditions of 24-hour hospital in December, 2020. In March, 2021 due to the appearance of new rashes, she returned to the FSBI "SSCDC", the Ministry of Health, where with regard to severity and prevalence of the skin patho-

Table 1. **Comparative data of clinical manifestations**
Таблица 1. **Сравнительные данные клинических проявлений**

Date	SCORAD	EASI	IGA
26.04.21	88 points	48,8 points	4 points
11.05.21	44,5 points	13,8 points	2 points

Table 2. **Comparison of laboratory data**
Таблица 2. **Сравнение данных лабораторных показателей**

Date	IgE total	Eosinophils	FeNO
27.04.21	1102,0 IU/ml	11 % (1188 cells/ml)	30 ppb
11.05.21	840 IU/ml	9 % (1070 cells/ml)	5 ppb

logical process Repeated therapy is recommended under the conditions of 24-hour hospital.

Since 24.03.21 she has got immunosuppressive therapy after another hospitalization (100 mg of Cyclosporin 1 capsule twice a day). Given torpidity and severity of the skin pathological process, it is suggested to consider prescribing the patient genetically engineered biological therapy in the case of failure of immunosuppressive therapy.

One month later, 26.04.2021, the patient was hospitalized in Rostov-on-Don for examining and starting genetically engineered biological therapy with dupilumab, regarding ineffective therapy.

The assessment of atopic dermatitis control in points upon admission to the hospital before dupilumab administration: on the SCORAD scale — 88 points; EASI — 48,8 points; IGA — 4 points.

The patient complained about skin rashes in the scalp area, face, neck, torso, upper and lower extremities, accompanied by severe itching, a feeling of tightness and burning of the skin.

Laboratory indicators: blood eosinophils (CBC) for 27.04.2021 — 11 % (1188 cells/microlitre). Total IgE — 1102,0 IU/ml.

27.04.2021: there was the measurement of exhaled nitric oxide (FeNO) — 30 ppb, with the norm from 0 to 19 ppb. And yet, the patient never reported signs of suffocation or coughing fits.

28.04.2021 dupilumab was administered at a dose of 600 mg (initial dose).

In 2 weeks, the patient was hospitalized to administer the second dose of the drug.

The assessment of atopic dermatitis control in points upon admission to the hospital 2 weeks after the administration of the first dose of dupilumab (Table 1): on the SCORAD scale — 44,5 points; EASI — 13,8 points; IGA — 2 points.

Laboratory indicators in 2 weeks (Table 2): eosinophils — 9 % (1070 cells/ml); total IgE — 840 МЕ/мл; FeNO — 5 ppb.

The patient gave consent to receive biological therapy and use the obtained results of the examination for scientific purposes.

Currently, the patient continues biological therapy. Atopic dermatitis is under control.

DISCUSSION

Literature data show that dupilumab, used in adolescents, causes significant improvements of symptoms in the 16th week (randomized placebo-controlled clinical trial (LIBERTY AD ADOL), in which 251 adolescents with severe and moderate atopic dermatitis received 300 mg of dupilumab every 4 weeks) [17]. In our clinical case significant improvement of clinical and laboratory parameters were observed within a week after starting biological therapy, using dupilumab. What allows to verify the drug efficacy and need for further research to produce new effective and convenient treatments of atopic dermatitis. Some studies have data on the early positive effect of dupilumab

application not only in atopic dermatitis, but also in severe bronchial asthma; the effect was noted in the first 2 weeks of the treatment [18].

It has previously been shown that dupilumab both decreases the incidence of new allergy and improves pre-existing allergic conditions [19]. It has also been proven that blocking signaling pathway of IL-4/IL-13 reduces the concentration of many of type 2 inflammatory markers, including IgE, periostin and multiple pro-inflammatory cytokines and chemokines (e.g., eotaxin, TARC) as well as decreases the level of fractional exhaled nitric oxide (FeNO) — the marker of inflammation in the lungs [20]. Due to a decrease in FeNO rate in the clinical case, we can assume that in the future FeNO rates should be evaluated in patients with atopic dermatitis to predict therapy efficiency in the prevention of bronchial asthma.

Biological therapy in its breakthrough action is comparable to antibiotic therapy and vaccination, innovative at the time. Undoubtedly, prospects of biological therapy in allergology are huge and not limited to symptom control. Dupilumab is a successful representative of its class of drugs with a highly favourable profile of efficacy and safety, enabling it to occupy an important niche in therapy of allergic diseases [21].

CONCLUSION

Dupilumab therapy has enabled the patient to achieve a significant improvement during atopic dermatitis:

1. There was clinical improvement on SCORAD, EASI and IGA evaluation index in two or more times;
2. A moderate decline in the level of eosinophils was noted during therapy: initially — 1188 cells/microlitre, in 2weeks — 1070 cells/ml;
3. There was a decrease in the level of total IgE: initially — 1102,0 IU/ml, in 2 weeks — 840 IU/ml;
4. Taking the drug contributed to a reduction in inflammation activity (reduction of FeNO from 30 to 5 ppb);
5. There was improvement in quality of life.

This clinical case makes us think about the prevention of bronchial asthma within the concept of "atopic march" by acting on key targets in immunopathogenesis of T2-associated diseases.

REFERENCE/ЛИТЕРАТУРА

1. Клинические рекомендации. Атопический дерматит. 2020. [Clinical guidelines Atopic dermatitis. 2020. (In Russ.)] https://www.nrcii.ru/specialistam/klinrecommend/atopic_dermatitis_2020.pdf
2. Хёгер Петер Г. Детская дерматология / пер. с нем. под ред. А. А. Кубановой, А. Н. Львова. Москва : Издательство Панфилова ; БИНОМ. Лаборатория знаний, 2013; с. 162–163. [Hyoger Peter G. Detskaya dermatologiya / per. s nem. pod red. A. A. Kubanovoj, A. N. L'vova. Moskva : Izdatel'stvo Panfilova ; BINOM. Laboratoriya znanij, 2013; s. 162–163. (In Russ.)]
3. Nakahara T, Kido-Nakahara M, Tsuji G, Furue M. Basics and recent advances in the pathophysiology of atopic dermatitis. The Journal of Dermatology. 2021; 48: 130–139. https://doi.org/10.1111/1346-8138.15664
4. Чурюкина ЭВ. Дупилумаб: аспекты применения при тяжелой бронхиальной астме в реальной клинической практике. Практическая пульмонология. 2022; 2: 3–10. [Churyukina EV. Dupilumab: aspects of use in severe bronchial asthma in real clinical practice. Practical pulmonology. 2022; 2: 3–10. (In Russ.)] https://doi.org/10.24412/2409-6636-2022-12937
5. Кузубова НА, Титова ОН. Т2-ассоциированные заболевания: в фокусе коморбидный пациент. Медицинский совет. 2020; (17): 57–64. [Kuzubova NA, Titova ON. T2-associated diseases: focus on the comorbid patient. Meditsinskiy sovet = Medical Council. 2020; (17): 57–64. (In Russ.)] https://doi.org/10.21518/2079-701X-2020-17-57-64
6. Передельская МЮ, Ненашева НМ, Передельский ЮА и др. Эффективность и безопасность дупилумаба у пациентки с Т2-ассоциированными заболеваниями. Практическая пульмонология. 2020; 3: 12–18. [Peredelskaya MYu, Nenasheva NM, Peredelskiy YuA et al. The Efficacy and Safety of Dupilumab in a Patient with T2-associated Diseases. Practical pulmonology. 2020; 3: 12–18. (In Russ.)] https://cyberleninka.ru/article/n/effektivnost-i-bezopasnost-dupilumaba-u-patsientki-s-t2-assotsiirovannymi-zabolevaniyami
7. Ревякина ВА, Геппе НА, Малахов АБ, и др. Биологические препараты в терапии атопического дерматита и бронхиальной астмы: фокус на дупилумаб. Педиатрия. Consilium Medicum. 2021; 2: 129–137. [Reviakina VA, Geppe NA, Malakhov AB et al. Biological drugs in the therapy of atopic dermatitis and bronchial asthma: focus on dupilumab. Pediatrics. Consilium Medicum. 2021; 2: 129–137. (In Russ.)] https://doi.org/10.26442/26586630.2021.2.201053
8. Себекина ОВ, Передкова ЕВ, Ненашева НМ и др. Биологическая терапия у пациента с тяжелым атопическим дерматитом. Клинический случай. Практическая аллергология. 2021; 1: 38–46. [Sebekina OV, Peredkova EV, Nenasheva NM, et al. Biological therapy in a patient with severe atopic dermatitis. Clinical case. Practical allergology. 2021; 1: 38–46. (In Russ.)] https://doi.org/10.46393/2712-9667_2021_1_38-46

9. Seegräber M, Srour J, Walter A, et al. Dupilumab for treatment of atopic dermatitis. Expert Rev Clin Pharmacol. 2018; 11: 467–74. https://doi.org/10.1080/17512433.2018.1449642
10. Harb H, Chatila TA. Mechanisms of dupilumab. Clin Exp Allergy. 2020; 50: 5–14. https://doi.org/10.1111/cea.13491
11. Alexis AF, Rendon M, Silverberg JI, et al. Efficacy of dupilumab in different racial subgroups of adults with moderate-to-severe atopic dermatitis in three randomized, placebocontrolled phase 3 trials. J Drugs Dermatol. 2019; 18: 804–813.
12. Wollenberg A, Beck LA, Blauvelt A, et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br J Dermatol. 2020; 182: 1120–1135. https://doi.org/10.1111/bjd.18434
13. Silverberg JI, Yosipovitch G, Simpson EL, et al. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. J Am Acad Dermatol. 2020; 82: 1328–1336. https://doi.org/10.1016/j.jaad.2020.02.060
14. Gade A, Ghani H, Rubenstein R. Dupilumab. Treasure Island (FL): Stat Pearls Publishing; 2024 Jan. https://www.ncbi.nlm.nih.gov/books/NBK585114/
15. Мурашкин НН, Опрятин ЛА, Епишев РВ, и др. Новая эра в лечении атопического дерматита: результаты длительного применения дупилумаба. Вопросы современной педиатрии. 2021; 20 (5): 390–395. [Murashkin NN, Opryatin LA, Epishev RV et al. New Era in Atopic Dermatitis Treatment: Results of Long-Term Dupilumab Administration. Issues of modern pediatrics. 2021; 20 (5): 390–395. (In Russ.)] https://doi.org/10.15690/vsp.v20i5.2312
16. Коннов ПЕ, Арсеньева АА. Эффективность и безопасность применения первого таргетного биологического препарата дупилумаб в терапии тяжелого непрерывно-рецидивирующего атопического дерматита. Вестник дерматологии и венерологии. 2023; 99 (1): 62–70. [Konnov PE, Arsenieva AA. Efficacy and safety of the first targeted biological drug dupilumab in the treatment of severe continuously relapsing atopic dermatitis. Vestnik Dermatologii i Venerologii. 2023; 99 (1): 62–70. (In Russ.)] https://doi.org/10.25208/vdv1384
17. Paller AS, Bansal A, Simpson EL, et al. Clinically Meaningful Responses to Dupilumab in Adolescents with Uncontrolled Moderate-to-Severe Atopic Dermatitis: Post-hoc Analyses from a Randomized Clinical Trial. Am J Clin Dermatol. 2020 Feb; 21 (1): 119–131. https://doi.org/10.1007/s40257-019-00478-y
18. Tani N, Kataoka N, Kunimatsu Y, et al. Early responders within seven days of dupilumab treatment for severe asthma evaluated by patient-reported outcome: a pilot study. Multidiscip Respir Med. 2021 Mar 17; 16 (1): 736. https://doi.org/10.4081/mrm.2021.736
19. Bieber T. In search of the Holy Grail in atopic dermatitis: Will dupilumab become the first disease-modifying atopic dermatitis drug? Allergy Clin Immunol. 2023 Mar; 151 (3): 694–696. https://doi.org/10.1016/j.jaci.2022.12.824
20. Murdoch JR, Lloyd CM. Chronic inflammation and asthma. Mutat Res. 2010; 1 (2): 24–39. https://doi.org/10.1016/j.mrfmmm.2009.09.005
21. Смолкин ЮС, Масальский СС, Смолкина ОЮ. Вопросы применения биологической терапии при атопическом дерматите: акцент на дупилумаб. Аллергология и иммунология в педиатрии. 2020; 61 (2): 27–40. [Smolkin YS, Masalsky SS, Smolkina OY. The application of the biological treatment in atopic dermatitis: focus on dupilumab. Allergology and Immunology in Pediatrics. 2020; 61 (2): 27–40. (In Russ.)] https://doi.org/10.24411/2500-1175-2020-10005

THE AUTHORS' CONTRIBUTION TO THE WORK

Ella V. Churyukina — curation, treatment of patients, review of literature, collection and analysis of literary sources, writing and editing the article.

Ekaterina A. Portnyaga — curation of patients, diagnostic monitoring of patients, review of literature, collection and analysis of literary sources, preparation and writing of the article.

All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

ВКЛАД АВТОРОВ В РАБОТУ

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Все авторы подтверждают соответствие своего авторства международным критериям ICMJE, все авторы внесли существенный вклад в разработку концепции, подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Consent for publication. Written consent for publication of relevant medical information within the manuscript was obtained from the patients and patient's parents.

Информированное согласие на публикацию. Пациенты и их законные представители добровольно подписали информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

Jacobsen's syndrome: case report

RAR — научная статья

https://doi.org/10.53529/2500-1175-2024-1-27-35

Received 12.02.2024
The article is accepted for publication 14.03.2024

Conflict of Interest:
The authors state that there is no external funding for the study.
The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Annotation

Introduction. Jacobsen syndrome (JS) is a rare genetic disease associated with the deletion of chromosome 11q, characterized by multiple malformations, hematological and immune disorders. The development of immunodeficiency in JS is often underestimated, which leads to recurrent infectious complications.

Presentation of a clinical case. The article presents a clinical case of a patient with a deletion of chromosome 11q and combined immunodeficiency. Our patient had recurrent infections, cytopenic syndrome, combined immunodeficiency, as well as other clinical manifestations of Jacobsen syndrome.

In addition to a decrease in serum immunoglobulins, a deep deficiency of the T-cell link of immunity with a low content of T-lymphocytes, recent emigrants from the thymus, has been established.

Conclusions. The peculiarity of the presented clinical case is that with a relatively small amount of deletion 11q, the child realized a complete clinical phenotype of the disease and a deep combined immunodeficiency. The article was written to improve doctors' knowledge about this rare form of congenital immunodeficiency.

Keywords: Jacobsen syndrome, del 11q, combined immunodeficiency.

For citation: Barycheva LYu, Bachieva LI, Koz'mova NA. Jacobsen's syndrome: case report. *Allergology and Immunology in Pediatrics.* 2024; 1: 27-35. https://doi.org/10.53529/2500-1175-2024-1-27-35

Синдром Якобсена: отчет о клиническом случае

https://doi.org/10.53529/2500-1175-2024-1-27-35

Статья поступила 12.02.2024
Статья принята в печать 14.03.2024
УДК 616-007-053.1:575.224.23

Конфликт интересов:
Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Аннотация

Введение. Синдром Якобсена (СЯ) — редкое генетическое заболевание, связанное с делецией хромосомы 11q, характеризующееся множественными пороками развития, гематологическими и иммунными расстройствами. Развитие иммунодефицита при СЯ часто является недооцененным, что приводит к рецидивирующим инфекционным осложнениям.

Изложение клинического случая. В статье приведено клиническое наблюдение пациента с делецией хромосомы 11q и комбинированным иммунодефицитом.

У нашего пациента отмечались рецидивирующие инфекции, цитопенический синдром, комбинированный иммунодефицит, а также другие клинические проявления синдрома Якобсена. Кроме снижения сывороточных иммуноглобулинов, установлен глубокий дефицит Т-клеточного звена иммунитета с низким содержанием Т-лимфоцитов — недавних эмигрантов из тимуса.

Заключение. Особенностью представленного клинического случая является то, что при сравнительно небольшом объеме делеции 11q у ребенка реализовался полный клинический фенотип заболевания и глубокий комбинированный иммунодефицит. Статья написана для улучшения знаний врачей об этой редкой форме врожденного иммунодефицита.

Ключевые слова: синдром Якобсена, синдром делеции 11q, комбинированный иммунодефицит.

Для цитирования: Барычева ЛЮ, Бачиева ЛИ, Козьмова НА. Синдром Якобсена: отчет о клиническом случае. *Аллергология и иммунология в педиатрии*. 2024; 1: 27-35. https://doi.org/10.53529/2500-1175-2024-1-27-35

INTRODUCTION. Jacobsen syndrome (JBS; MIM 147791), also known as the syndrome of terminal deletion 11q, is a rare genetic disease, caused by the loss of continuous set of genes in the long arm of chromosome 11 [1, 2, 3]. The disease occurs in 1 per 100 000, with a ratio of women to men 2:1 [4, 5]. 85 % of recorded cases arise by mutation de novo [4].

Since the first description of Jacobsen syndrome in 1973 there have been more than 200 recorded cases, characterized by deletions and affecting telomeric regions of chromosome 11. The size of the deletion is 7–20 Mb and the proximal breaking point is inside or closer to the telomeric end of the sub-band 11q23.3 [6, 7, 8]. This terminal haploinsufficiency might affect the function of more than 100 different genes. The diagnosis of complete syndrome is established when BSX, NRGN, ETS-1, FLI-1 and RICS (ARHGAP32) genes are involved in the deletion. Patients with smaller deletions have a partial phenotype [2, 6]. Variability of phenotype-genotype might be associated with incomplete penetrance as well as with other genes of interest, located on 11q, such as TIRAP, FLI-1, NFRKB, THYN1 and SNX19 [9].

The disease covers a wide range of clinical manifestations. Studies show that 97 % of patients have from mild to severe mental retardation. The degree of neurocognitive disorder is closely associated with the size of the deletion [5, 10].

Platelet abnormalities occur in 88,5–94% of cases. There is noted neonatal thrombocytopenia that may resolve with time, and platelet dysfunction of long-lasting nature [11]. There is an increased number of small megakaryocytes (micromegakaryocytes) and their delayed maturation in the bone marrow [12].

Congenital heart defects, most often, defects of the interventricular septum and left-side obstructive lesions, are found in 56 % of patients, and they are the most common cause of death [5, 7]. Hypoplastic left heart syndrome, one of the most severe congenital heart diseases, is described in 5–10 % of patients with Jacobsen syndrome (compared to 0,02 % in the general population) [13]. Studies in humans and mice showed that ETS-1 gene, located in a “cardiac critical area” on the terminal part of chromosome 11, is the cause of congenital heart disease [2, 13].

Craniofacial dysmorphism (> 40 %) is often manifested in the form of trigonocephaly, ocular hypertelorism, strabismus, eyelid ptosis, coloboma of the iris and wide nose bridge. There is skin syndactyly on the hands, abnormal palmar crease and hypoplastic thenar space. Feet are short, flat with syndactyly of the 2nd and 3rd toes [5, 7].

In 2004 P. D. Grossfeld and colleagues conducted the prospective analysis of 110 patients with the syndrome of terminal deletion 11q. There were no clear signs of immunodeficiency, no recorded life-threaten-

List of abbreviations/список сокращений:

BSX:	brain specific homeobox
ETS-1:	proto-oncogene 1, transcription factor
FLI-1:	proto-oncogene, ETS transcription factor
JAM3:	junctional adhesion molecule 3
KREC:	kappa-deleting recombination excision circle
NFRKB:	nuclear factor related to kappaB binding protein
NRGN:	neurogranin
RICS:	Rho GTPase activating protein 32
SNX19:	sorting nexin 19
THYN1:	thymocyte nuclear protein 1
TIRAP:	TIR domain containing adaptor protein
TREC:	T-cell receptor excision circle
ADP:	adenosine diphosphate
IVIG:	intravenous immunoglobulin
CHD:	congenital heart disease
DIVS:	defect of the interventricular septum
DISS:	defect of the interstitial septum
IUGR:	intrauterine growth retardation
DC:	disturbed circulation
AS:	Apgar score
SCIG:	subcutaneous immunoglobulin
JS:	Jacobsen syndrome
FC:	functional class
CKD:	chronic kidney disease

ing and (or) opportunistic infections in the studied cohort. However, recurrent episodes of otitis media and (or) sinusitis were frequent and observed in 42 out of 78 patients (54 %) [5].

The first immune defect, recorded in this syndrome, was antibody deficiency [14]. A number of studies have noted a decrease in all classes of immunoglobulins (IgA, IgM, IgG) and disorder of specific antibody formation in response to vaccination with pneumococcal polysaccharide vaccine, which is typical for patients with common variable immunodeficiency [15]. The mechanism by which the terminal deletion of chromosome 11 contributes to the development of immunodeficiency is not fully understood. It is assumed that immunodeficiency occurs mainly due to ETS (ETS-1) or FLI-1 gene loss. ETS-1 is highly expressed in NK-cells, B- and T-lymphocytes and involved in the development of NK-cells, differentiation of T- and B-lymphocytes [16, 17, 18].

Only in 2020 the disease was considered as congenital immune system defect and included in the classification of primary immunodeficiencies, namely in the group of combined primary immunodeficiency states with syndromic manifestations [19].

DESCRIPTION OF THE CLINICAL CASE

Here we present a clinical case of a patient aged 7 with diagnosed Jacobsen syndrome. The patient's parents gave consent to the use of information, including the child's photo, in research and publication.

The boy K. Was born from the second pregnancy, second birth, in the 37th week of gestation. Heart disease was recorded parenterally at 18 weeks. Birth weight is 2030 g, length — 46 cm, AS (Apgar score) — 7/8 points. Tetralogy of Fallot is diagnosed in the neonatal period (aortic dextroposition, membranous ventricular septal defect up to 6,9 mm, secondary defect of interatrial septum up to 5,0 mm, interventricular septum hypertrophy). Circulatory failure – 1B. FC 2 (NYHA). There is intrauterine growth retardation of grade III, abnormalities of the facial skeleton. Radical correction of double-outlet right ventricle was carried out at the age of 10 months.

Due to congenital anomaly, the child has been examined by a geneticist, inherited metabolic diseases are excluded, the normal male karyotype is established (46 XY), dysplastic phenotype has been ascertained: facial dysmorphism, trigonocephaly, hypertelorism, antimongoloid slant, ptosis, highly arched palate, anomaly of the external auditory canal on the left, sparrow chest (fig. 1).

Psychomotor retardation, restless behaviour, sleep disruption and autoaggression were observed from the first month of life. The patient was observed by the neurologist with the diagnosis "Symptomatic epilepsy". Mental retardation. Behavioral disorders. Alalia. At the age of 7 the patient has sign language, says single words, does not fix attention; there is motor awkwardness and a significantly limited scope of actions.

Polycystic left kidney, 1-2 degree of chronic kidney disease, is diagnosed at the age of 5. At an early

Рис. 1. **Признаки лицевого дисморфизма: тригоноцефалия, широкая переносица, гипертелоризм глаз, птоз, низко посаженные ушные раковины, тонкая верхняя губа**
Fig. 1. **Signs of facial dysmorphic disorder: trigonocephaly, wide bridge of the nose, hypertelorism of the eyes, ptosis, low-set auricles, thin upper lip**

age the by experienced frequent respiratory infections — ARVI (up to 9 times per year), pleural and purulent otitis media, bronchitis, poor weight gain. Till the age of 3 there were 4 reported episodes of purulent otitis; he was hospitalized twice with bronchopneumonia, got repeated antibiotic therapy (at least 4 per year). From 1 year 4 months complete blood count has revealed thrombocytopenia in the range of 78–88*10^9/l, leukopenia — 3,3–1,6*10^9/l. At the age of 3 the boy came to the attention of the allergist-immunologist of the Regional Children's Clinical Hospital in Stavropol, there was a significant reduction in TREC (T-cell receptor excision circle) rates, all populations of T-lymphocytes, hypoimmnoglobulinemia (Table 1). Given a distinctive phenotype, primary immunodeficiency, DiGeorge syndrome, was suspected. However, parathyroid hormone and ionized calcium were within reference values. Substitution therapy with intravenous immunoglobulins (IVIG) was initiated, followed by subcutaneous immunoglobulin (SCIG); preventive antimicrobial therapy (cotrimoxazole, fluconazole, azithromycin) was prescribed.

To clarify the diagnosis in FSBI Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, fluorescence in situ hybridization FISH on chromosome 22 was conducted, however, 22q11.2 deletion was not found. The child's blood was sent for NGS-sequencing (next generation sequencing), "immunological panel". There was a two-fold reduction in reads of all FLI-1 gene exons, localized on chromosome 11 that pointed to deletion of one of the two gene copies. When specifying the size of the defect by molecular genetic microarray, there was identified terminal deletion on the region of chromosome 11 11q24.2q25 at a size of 10084933 base pairs with coverage of 44 genes in the imbalance region as well as microduplication of chromosome 16 16p13.11 at a size of 14435773 base pairs (31 genes) and chromosome 22 22q13.31q13.33 with a length of 6730554 base pairs (52 genes) that indicated an unbalanced translocation between *11q* and *22q* with high probability. The child got the confirmed rare syndromal immunodeficiency: Jacobsen syndrome. Paris-Trousseau thrombocytopenia. The number of genes in the imbalanced region included the genes, responsible for the development of immune responses (TIRAP, FLI-1, JAM3).

In order to estimate our patient's immune dysfunction, we have analyzed levels of immunophenotyping and serum immunoglobulins during the 4-year follow-up (Table 1). There is a critical decrease in TREC and KREC ("BT test" ("Generium", Russia)), persistent T-cell immunodeficiency with a decrease in the level of total T-lymphocytes, T-helper cells, T-cytotoxic lymphocytes. A reduction in naive T-helper

Table 1. **Investigation of subpopulations T-, B-lymphocytes, immunoglobulins and platelets in a patient with Jacobsen syndrome**
Таблица 1. **Исследование субпопуляций Т- и В-лимфоцитов, иммуноглобулинов и тромбоцитов у пациента с синдромом Якобсена**

Indicators	3 years	5 years	6 years	7 years	Norm
Leukocytes*10^9/l	3,8	2,23		3,5	6,1–9,9
Lymphocytes/μl	1216	820	590	1,2	1,5–7,0
T-cell $CD3^+$/μl	510	500	650	420	900–4500
Helper T-cell $CD3^+CD4^+$/μl	310	300	460	290	500–2400
Naive helper T-cell $CD3^+CD4^+CD45^+CD197^-$/μl		46,5	53		200–2500
Memory helper T-cell TEMRA $CD3^+CD4^+CD45^+CD197^-$/μl		15,3	66,6		0,025–25
Cytotoxic T-cell $CD3^+CD8^+$/μl	150	140	160	110	300–1600
Naive cytotoxic T-cell $CD3^+CD8^+CD45^+CD197^+$/μl		34,1	40,3		42–1300
Memory cytotoxic T-cell TEMRA $CD3^+CD8^+CD45^+CD197^-$/μl		58,7	37,9		57–340
B-cell $CD19^+$/μl	280	100	120	120	200–2100
Naive B-cell $IgD^+IgM^+CD27^-$/μl		75	91		147–431
Switched memory B-cell $IgD^-IgM^-CD27^+$/μl		5	5,2		31–94
NK-cell $CD16^+CD56^+$/μl	360	250		160	100–1000
TREC/μl	1,9	2,9	0		30–327
KREC/μl	48,1	36	20,9		75–541
IgA (g/l)	0,31	0,27	0,28	0,41	0,9–1,9
IgM (g/l)	0,34	0,17	0,12	0,2	0,8–1,9
IgG (g/l)	2,9	5,52	8,79	9,0	8,7–11,7
Platelets*10^9/l	60	80	78	95	204–356

cells and T-cytotoxic T-lymphocytes as well as naive B-lymphocytes and switched memory B-lymphocytes (Switched memory B-cell) was shown. The reduction of these indicators was combined with hypoimmunoglobulinemia.

Levels of B-lymphocytes, serum IgA and IgM remained low throughout the follow-up period. IgG levels were normalized due to regular replacement IVIG/SCIG therapy.

Given the presence of FLI-1 gene deletion, causing the development of thrombocytopenia with dense platelet granule defect, there was functional platelet study — a decrease in platelet aggregation with ristocetin up to 29 % and adrenaline to 38% was noted, aggregation with ADP (adenosine diphosphate) was within normal limits — 36 %.

Serious systemic infectious diseases were not revealed against the background of preventive therapy.

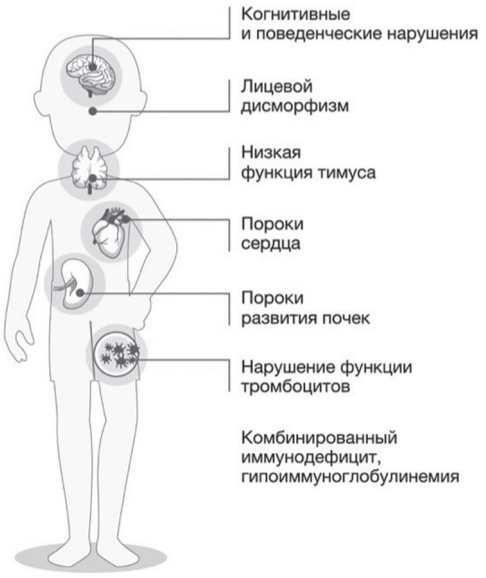

Fig. 2. **Clinical features of Jacobsen syndrome**
Рис. 2. **Клинические особенности синдрома Якобсена**

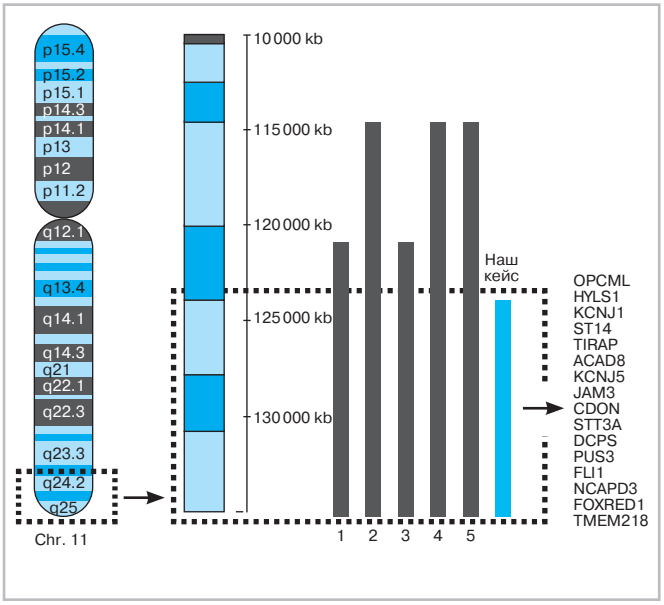

Fig. 3. **Deletion *11q24.2q25* in a patient with partial Jacobsen syndrome. On the left is chromosome 11 with a critical region of deleted genes in comparison with deletions described in available sources [5, 20, 21, 22, 24]. On the right are the deleted genes**
Рис. 3. **Делеция *11q24.2q25* у пациента с частичным синдромом Якобсена. Слева — хромосома 11 с критической областью удаленных генов в сравнении с делециями, описанными в доступных источниках [5, 20, 21, 22, 24]. Справа — удаленные у пациента гены**

DISCUSSION

Jacobsen syndrome is a rare form of a genetic disease that has recently been classified as primary combined immunodeficiency [15, 19].

The presented case corresponded to the complete clinical phenotype of the disease, despite the genetic traits of partial Jacobsen syndrome. Our patient experienced typical dysmorphic features such as low growth, microcephaly, facial skeleton anomaly, congenital heart disease, chronic kidney disease, mental retardation, cytopenic syndrome (fig. 2).

In recent years, researchers have focused on genotype-phenotype correlations as well as candidate gene reading, responsible not only for cognitive impairment and multiple malformations in patients with Jacobsen syndrome, but also for immune defects [20, 33]. The deletion level in Jacobsen syndrome may vary (fig. 2). Its level in our clinical case is much lower, in comparison with the deletions, described in other sources (fig. 3).

Three genes in the deleted region 11q24.2q25 were associated with the defect in immune regulation (FLI-1, TIRAP, JAM3).

It is known that FLI-1 encodes a transcription factor, specific to erythroblast transformation. However, FLI-1 heterozygous deletion might cause dysmegakaryopoiesis, functional disorders of T-lymphocytes, deficiency of T-helper cells and a low level of serum IgM [23, 24, 25] that is confirmed in experimental models [26]. It was found that FLI-1 gene modulates a marginal zone follicular B-cell development in mice [27]. Previously it was shown that patients with Jacobsen syndrome are quite often the holders of FLI-1 gene deletion [2, 28, 29, 30]. FLI-1 gene haploinsufficiency was has been suggested as a genetic change, responsible for immune system defects in Jacobsen syndrome.

The number of gene in the imbalance area also included TIRAP genes (607948, 611162, 614382),

encoding signaling protein of Toll-like receptors — TLR2 и TLR4. For the past two decades, their key role in reactions of the innate immune response on bacterial lipopolysaccharides has been determined and their relevance in antitumor immunity has been confirmed [31].

JAM3 gene is part of the family of connective-tissue adhesion molecules with high expression on the cell surface of T-cytotoxic lymphocytes and activated cells. Besides, there is a large number of JAM3 molecule, presented on megakaryocytes and platelets that implies its part in the inflammatory process, mediated by monocytes [2].

Immunological data on patients with Jacobsen syndrome in the world is significantly limited, however, there are accumulated reports on serious disorders in the process of maturation and differentiation of all compartments of T- и B-lymphocytes in the syndrome of terminal deletion 11q [32].

Our patient has experienced persistent impairment of the T-cell component of immunity and antibody formation for 4 years of observation.

Previous studies have showed that T-lymphocyte reduction and [28, 32] their functional defects [15, 20] are observed in the majority of patients with 11q disorder that is often accompanied by hypersensitivity to persistent herpes viruses CMV, HSV1, VZV, human papilloma virus [34].

In the work of Baronio M. and colleagues (2022) 66,7 % of patients with JS had a defined reduction in $CD3^+$-cells, 58,3 % — T-helpers. Naive T-helpers were low in 45,4% of patients, TREC rates — in 88,9 % [32].

Data on a decrease in the total number of B-lymphocytes as well as immunoglobulins in patients with JS were first published back in 1998 [33]. Several studies have shown hypoimmunoglobulinemia with reduced IgG, IgA, IgM and disorder of specific antibody formation in response to pneumococcal polysaccharide vaccine that is compatible with the phenotype of common variable immunodeficiency [15]. The literature describes clinical cases of adult patients with humoral immunodeficiency manifestations, which exacerbated over time [23, 34]. For example, a girl with JS has suffered from recurrent sinopulmonary infections since the age of 18, she experienced a decreased IgG level, a low number of switched memory B-cells as well as disorder of specific antibody formation [34]. A low number of B-lymphocytes with $IgD^-IgM^-CD27^+$ phenotype is also noted in other studies [15] which has coincided with the obtained data.

Depending on eliminated genes, various immunological phenotypes can be observed, however, their correlation with deletions of particular genes, situated in 11q region, are not well understood. Trachsel T. And colleagues (2022 г.) described a patient with JS and severe primary immunodeficiency, who had decreasев antibody titers against *Haemophilus influenza*, content of B-lymphocytes and switched memory B-cells. Another patient with heterozygous deletion of TIRAP, FLI-1, NFRKB, THYN1 and SNX19 suffered a severe bacterial infection, had predominantly a low number of switched memory B-cells [30]. There is an opinion that clinical manifestations of immunodeficiency in patients with JS can have varying degrees of severity, however, they increase with age in the absence of treatment [23, 28, 34, 35].

CONCLUSION

Patients with partial 11q deletion have a high risk of inborn immunity errors due to loss the genes, responsible for immune responses, which function is only being studied. The presented clinical case in conjunction with literature data demonstrates the importance of immunological observation of patients with JS. We have shown that even quite small 11q deletion might cause the formation of severe combined immunodeficiency, that's why patients with JS require a regular immunological screening by lymphocyte immunophenotyping as well as defining serum immunoglobulins. It should be noted that immunological disorders might develop over time and require to be re-tested. In case of quantitative and qualitative defect of T- and B-lymphocytes as well as serious infectious complications, it is necessary to consider preventive administration of antibacterial agents and replacement therapy with immunoglobulin preparations.

REFERENCE/ЛИТЕРАТУРА

1. Ferrigno F, Franceschini A, Kirk R, Amodeo A. Jacobsen Syndrome with Hypoplastic Left Heart Syndrome: Outcome after Cardiac Transplantation. J Cardiovasc Dev Dis. 2022 Dec 24; 10 (1): 8. https://doi.org/10.3390/jcdd10010008.
2. Rodríguez-López R, Gimeno-Ferrer F, Montesinos E et al. Immune Deficiency in Jacobsen Syndrome: Molecular and Phenotypic Characterization. Genes (Basel). 2021 Jul 31; 12 (8): 1197. https://doi.org/10.3390/genes12081197.
3. Yalcintepe S, Zhuri D, Sezginer Guler H et al. First Report of Jacobsen Syndrome with Dextrocardia Diagnosed with del(11)(q24q25). Mol Syndromol. 2022 May; 13 (3): 235–239. https://doi.org/10.1159/000519149.
4. Chen CP, Wang LK, Wu PC et al. Molecular cytogenetic characterization of Jacobsen syndrome (11q23.3-q25 deletion) in a fetus associated with double outlet right ventricle, hypoplastic left heart syndrome and ductus venosus agenesis on prenatal ultrasound. Taiwan J Obstet Gynecol. 2017 Feb; 56 (1): 102–105. https://doi.org/10.1016/j.tjog.2016.12.004.
5. Grossfeld PD, Mattina T, Lai Z et al. The 11q terminal deletion disorder: a prospective study of 110 cases. Am J Med Genet. 2004; 129A: 51–61. https://doi.org/10.1002/ajmg.a.30090.
6. Favier R, Akshoomoff N, Mattson S, Grossfeld P. Jacobsen syndrome: Advances in our knowledge of phenotype and genotype. Am J Med Genet C Semin Med Genet. 2015 Sep; 169 (3): 239–250. https://doi.org/ 10.1002/ajmg.c.31448.
7. Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet J Rare Dis. 2009 Mar 7; 4: 9. https://doi.org/
8. Fujino S, Yoshihashi H, Takeda R et al. White matter abnormality in Jacobsen syndrome assessed by serial MRI. Brain Dev. 2020 Sep; 42 (8): 621–625. https://doi.org/10.1016/j.braindev.2020.05.001.
9. Anzick S, Thurm A, Burkett S et al. Chromoanasynthesis as a cause of Jacobsen syndrome. Am J Med Genet A. 2020 Nov; 182 (11): 2533–2539. https://doi.org/10.1002/ajmg.a.61824.
10. Coldren CD, Lai Z, Shragg P et al. Chromosomal microarray mapping suggests a role for BSX and Neurogranin in neurocognitive and behavioral defects in the 11q terminal deletion disorder (Jacobsen syndrome). Neurogenetics. 2009 Apr; 10 (2): 89–95. https://doi.org/10.1007/s10048-008-0157-x.
11. Favier R, Jondeau K, Boutard P et al. Paris-Trousseau syndrome: clinical, hematological, molecular data of ten new cases. Thromb Haemost. 2003 Nov; 90 (5): 893–897. https://doi.org/10.1160/TH03-02-0120.
12. Gangarossa S, Schiliró G, Mattina T et al. Dysmegakaryopoietic thrombocytopenia in patients with distal chromosome 11q deletion. Blood. 1996 Jun 1; 87 (11): 4915–4916. PMID: 8639871.
13. Herrick NL, Lamberti J, Grossfeld P, Murthy R. Successful Management of a Patient With Jacobsen Syndrome and Hypoplastic Left Heart Syndrome. World J Pediatr Congenit Heart Surg. 2021 May; 12 (3): 421–424. https://doi.org/10.1177/2150135118822678.
14. Puglisi G, Netravali MA, MacGinnitie AJ, Bonagura VR. 11q terminal deletion disorder and common variable immunodeficiency. Ann Allergy Asthma Immunol. 2009 Sep; 103 (3): 267–268. https://doi.org/ 10.1016/S1081-1206(10)60192-5.
15. Dalm VA, Driessen GJ, Barendregt BH et al. The 11q Terminal Deletion Disorder Jacobsen Syndrome is a Syndromic Primary Immunodeficiency. J Clin Immunol 2015; 35 (8): 761–768. https://doi.org/10.1007/ s10875-015-0211-z.
16. Barton K, Muthusamy N, Fischer C et al. The Ets-1 transcription factor is required for the development of natural killer cells in mice. Immunity. 1998 Oct; 9 (4): 555–563. https://doi.org/10.1016/s1074-7613(00)80638-x.
17. Bories JC, Willerford DM, Grévin D et al. Increased T-cell apoptosis and terminal B-cell differentiation induced by inactivation of the Ets-1 proto-oncogene. Nature. 1995 Oct 19; 377 (6550): 635–638. https://doi.org/10.1038/377635a0.
18. Muthusamy N, Barton K, Leiden JM. Defective activation and survival of T cells lacking the Ets-1 transcription factor. Nature. 1995 Oct 19; 377 (6550): 639–642. https://doi.org/10.1038/377639a0.
19. Tangye SG, Al-Herz W, Bousfiha A et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 2020; 40 (1): 24–64. https://doi.org/10.1007/s10875-019-00737-x.
20. Blazina Š, Ihan A, Lovrečić L, Hovnik T. 11q terminal deletion and combined immunodeficiency (Jacobsen syndrome): Case report and literature review on immunodeficiency in Jacobsen syndrome. Am J Med Genet A. 2016 Dec; 170 (12): 3237–3240. https://doi.org/10.1002/ajmg.a.37859.
21. Penny LA, Dell'Aquila M, Jones MC et al. Clinical and Molecular Characterization of Patients with Distal 11q Deletions. Am J Hum Genet. 1995; 56: 676–683.
22. Akshoomoff N, Mattson SN, Grossfeld PD. Evidence for autism spectrum disorder in Jacobsen syndrome: Identification of a candidate gene in distal 11q. Genet. Med. 2015; 17: 143–148. https://doi.org/10.1038/gim.2014.86.
23. Von Bubnoff D, Kreiss-Nachtsheim M, Novak N et al. Primary immunodeficiency in combination with transverse upper limb defect and anal atresia in a 34-year-old patient with Jacobsen syndrome. Am J Med Genet A. 2004 Apr 30; 126A (3): 293–298. https://doi.org/10.1002/ajmg.a.20592.

24. Bernaciak J, Szczaluba K, Derwinska K et al. Clinical and molecular-cytogenetic evaluation of a family with partial Jacobsen syndrome without thrombocytopenia caused by an ~5 Mb deletion del(11) (q24.3). Am J Med Genet. 2008; 146A: 2449–2454. https://doi.org/10.1002/ajmg.a.32490.
25. Fujita H, Yanagi T, Kosaki R et al. Transverse limb defect in a patient with Jacobsen syndrome: Concurrence of malformation and disruption. Am J Med Genet. 2010; 152A: 1033–1035. https://doi.org/10.1002/ajmg.a.33151.
26. Hart A, Melet F, Grossfeld P et al. Fli-1 Is Required for Murine Vascular and Megakaryocytic Development and Is Hemizygously Deleted in Patients with Thrombocytopenia. Immunity. 2000; 13: 167–177. https://doi.org/10.1016/S1074-7613(00)00017-0.
27. Zhang XK, Moussa O, La Rue A et al. The transcription factor Fli-1 modulates marginal zone and follicular B cell development in mice. J Immunol. 2008 Aug 1; 181 (3): 1644–1654. https://doi.org/10.4049/jimmunol.181.3.1644.
28. Huisman EJ, Brooimans AR, Mayer S et al. Patients with Chromosome 11q Deletions Are Characterized by Inborn Errors of Immunity Involving both B and T Lymphocytes. J Clin Immunol. 2022 Oct; 42 (7): 1521–1534. https://doi.org/10.1007/s10875-022-01303-8.
29. Haghi M, Dewan A, Jones KL et al. Endocrine abnormalities in patients with Jacobsen (11q-) syndrome. Am J Med Genet A. 2004 Aug 15; 129A (1): 62–63. doi: 10.1002/ajmg.a.30248.
30. Trachsel T, Prader S, Steindl K et al. Case report: ETS1 gene deletion associated with a low number of recent thymic emigrants in three patients with Jacobsen syndrome. Front Immunol. 2022 Oct 21; 13: 867206. https://doi.org/10.3389/fimmu.2022.867206.
31. Papadakos SP, Arvanitakis K, Stergiou IE et al. The Role of TLR4 in the Immunotherapy of Hepatocellular Carcinoma: Can We Teach an Old Dog New Tricks? Cancers (Basel). 2023 May 17; 15 (10): 2795. https://doi.org/10.3390/cancers15102795.
32. Baronio M, Saettini F, Gazzurelli L et al. Immunological Evaluation of Patients Affected with Jacobsen Syndrome Reveals Profound Not Age-Related Lymphocyte Alterations. J Clin Immunol. 2022; 42 (2): 365–374. https://doi.org/10.1007/s10875-021-01169-2.
33. Sirvent N, Monpoux F, Pedeutour F et al. Jacobsen syndrome, thrombopenia, and humoral immunodeficiency. Arch Pediatr 1998; 5 (12): 1338–1340. https://doi.org/10.1016/s0929-693x(99)80052-9
34. So J, Stockley T, Stavropoulos DJ. Periventricular nodular heterotopia and transverse limb reduction defect in a woman with interstitial 11q24 deletion in the Jacobsen syndrome region. Am J Med Genet A 2014; 164A (2): 511–515. https://doi.org/10.1002/ajmg.a.36292.
35. Кузьменко НБ, Швец ОА, Мухина АА. Редкий случай комбинированного иммунодефицита с делецией длинного плеча хромосомы 11(q) — синдром Якобсена. Вопросы гематологии/онкологии и иммунопатологии в педиатрии. 2020; 19 (3): 114–120. [Kuz`menko NB, Shvetz OA, Muhina AA. Redkij sluchaj kombinirovannogo immunodeficita s deleciej dlinnogo plecha xromosomy 11(q) — sindrom Yakobsena. Voprosy` gematologii/onkologii i immunopatologii v pediatrii. 2020; 19 (3): 114–120. (In Russ.)] https://doi.org/10.24287/1726-1708-2020-19-3-114-120.

THE AUTHORS' CONTRIBUTION TO THE WORK

Liudmila Yu. Barycheva — concept of the article, text development, literature review, editing.
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ВКЛАД АВТОРОВ В РАБОТУ:

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Бачиева Л. И. — обзор литературы, написание текста, перевод на английский язык.
Козьмова Н. А. — наблюдение за пациентом, лабораторное обследование.

Consent for publication. The patient's legal representative voluntarily signed an informed consent to the publication of personal medical information in an impersonal form.

Информированное согласие на публикацию. Законный представитель пациента добровольно подписал информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

Following the X All-Russian Congress of the Association of Pediatric Allergologists and Immunologists of Russia (APAIR)

По следам X Всероссийского Конгресса Ассоциации детских аллергологов и иммунологов России (АДАИР)

Diagnostic significance of the determination of antinuclear antibodies in children with autoimmune hepatitis

SCO — краткое сообщение

https://doi.org/10.53529/2500-1175-2024-1-36-40

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Keywords: children, autoimmune hepatitis, liver fibrosis, antinuclear antibodies, HEp-2, autoimmunity, immunofluorescence.

For citation: Zhuzhula AA, Kurbatova OV, Petrichuk SV, Parakhina DV, Snovskaya MA, Movsisyan GB, Semikina EL, Potapov AS, Fisenko AP. Diagnostic significance of the determination of antinuclear antibodies in children with autoimmune hepatitis *Allergology and immunology in pediatrics*. 2024; 1: 36-40. https://doi.org/10.53529/2500-1175-2024-1-36-40

Диагностическая значимость определения антинуклеарных антител у детей с аутоиммунным гепатитом

https://doi.org/10.53529/2500-1175-2024-1-36-40

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Ключевые слова: дети, аутоиммунный гепатит, фиброз печени, антинуклеарные антитела, HEp-2, аутоиммунитет, иммунофлюоресценция.

Для цитирования: Жужула АА, Курбатова ОВ, Петричук СВ, Парахина ДВ, Сновская МА, Мовсисян ГБ, Семикина ЕЛ, Потапов АС, Фисенко АП. Диагностическая значимость определенияантинуклеарных антител у детей саутоиммунным гепатитом. *Аллергология и иммунология в педиатрии*. 2021; 1: 36-40. https://doi.org/10.53529/2500-1175-2024-1-36-40

INTRODUCTION

Autoimmune hepatitis (AIH) is an autoimmune inflammatory liver disease, causing the formation of autoaggressive antibodies to own hepatocytes [1]. AIH is considered a rare disease, its prevalence is 3–17 cases per 100000 population in Europe and the USA [2, 3, 4]. In Russia the percentage of AIH is 1,5–7 % [2, 4, 5] in the structure of chronic hepatitis in children. The disease often occurs in children aged 6–10, and it predominantly affects females [4, 5].

AIH etiology is not fully understood [4]. The violation of immunoreactivity in genetically predisposed individuals is considered a major cause of AIH development [2]. AIH triggers might be Epstein-Barr, hepatitis (A, B, C, D, G) and herpes simplex viruses, bacteria, drugs (interferon drugs, non-steroid anti-inflammatory drugs, nitrofurans, etc.), environmental factors [2, 4]. In the presence of a genetic predisposition there is impaired immune regulation, manifested by the defect in the function of T-cells [4]. The syn-

thesis of B-cells of the IgG class antibodies intensifies with AIH, which might cause the membrane destruction of normal hepatocytes [4].

One of the criteria for AIH diagnosis is the presence of antinuclear antibodies (ANA) in the blood serum, that are detected in 65– 78 %of patients with AIH [5, 6]. ANA is not detected in about 10 % of patients with AIH, but their absence does not exclude the diagnosis [6]. The "gold standard" and main screening method of laboratory diagnosis for detecting ANA in the blood serum is the reaction of indirect immunofluorescence (RNIF) on the cell line HEp-2 [3, 7]. The test result is information on the final titer of ANA and the type of nucleus fluorescence and cytoplasm of HEp-2 cells [7].

Detecting ANA in adults with AIH is accompanied by homogeneous (34–58 %), granule (21–34 %) and cytoplasmic (27 %) types of fluorescence or a combination of several types [6]. It is shown that the highest ANA titers in adults with AIH are noted in concomitant syndrome with primary biliary cirrhosis [6]. ANA studies in AIH against the backdrop of pathogenetic treatment in childhood have not been conducted.

Thus, the objective of our study was to define the diagnostic significance of a titer and types of ANA fluorescence in children with AIH during treatment.

MATERIALS AND METHODS

The study involved 77 children with AIH (42 girls and 35 boys), who were screened and treated in FSAI "NMRC for Children's Health" of the Ministry of Health of the Russian Federation. 65 of them were diagnosed with AIH type 1, 8 children — AIH type 2, 4 — seronegative AIH. Patients with AIH type 1 had comorbid diseases: AIH + primary sclerosing cholangitis (PSC) in 20 % of cases, AIH + autoimmune cholangitis (AIC) — in 12 %, AIH + multiple autoimmune pathologies — in 15 %. In the treatment dynamics 16 children were screened in 6 months — 1 year of standard therapy. The patient age changed from 1,91 to 17,97 years. All the children under treatment were examined on the standard protocol, including complete blood count (hematological automatic analyzer Sysmex XN 550, Japan), biochemical blood test (AU680, USA), ANA on the cell line HEp-2 by RNIF (Immco Diagnostics, Inc., USA).

RNIF method is based on incubation of patients' blood serum in serial dilutions with epithelial cells of adenocarcinoma in the person's larynx (HEp-2) in wells of a glass slide. After removing unbound components with the wash buffer, FITC conjugate was added to wells of a glass slide, which coloured bound antibodies. The result of the reaction was evaluated using fluorescence microscope Nikon Eclipse Ni (Japan) at a magnification of ×40. A maximum titer of detecting ANA and type of cell fluorescence were analyzed. ANA titers < 1/160 were considered as normal values, with the titer 1/160 the response was low-positive, 1/320–1/640 — moderate-positive, 1/1280 and higher — high-positive. We considered any detected type of ANA fluorescence as a positive result. To diagnose the liver fibrosis stage, the method of liver transient elastography was used on FibroScan F502 device (EchoSence, France). METAVIR scale was used to evaluate the severity of the degree of liver fibrosis: F0 stage— density in the range 1,5–5,8 kPa; F1 — 5,9–7,2 kPa; F2 — 7,3–9,5 kPa; F3 — 9,6–12,5 kPa; F4 stage (liver cirrhosis) — density 12,6 kPa and more [8, 9]. The distribution by the stages of liver fibrosis was: F0 — 11 patients (14 %), F1 — 14 (18 %), F2 — 13 (17 %), F3 — 9 (12 %), F4 — 30 детей (39 %).

Statistical processing of the results was carried out using Statistica 10.0 program (StatSoft, USA), Excel (Microsoft, USA), IBM SPSS Statistics 25 (USA). Descriptive statistics of quantitative traits is presented in the format: median [lower and upper quartiles] — Me [$Q_{0,25}$–$Q_{0,75}$].

RESULTS

Conducted analysis of ANA study results in children with AIH revealed that 8 children (10 %) had the titer 1/160, 14 (18 %) — 1/320, 9 (12 %) — 1/640, 19 (25 %) — 1/1280, 15 (20 %) — > 1/2560, and 12 patients out of 77 (15 %) did not have antibodies.

Analysis revealed that children with AIH often had the following types of ANA fluorescence: cytoplasmic (74 %), granular (63 %) and homogeneous (57 %). Combined, dots in the nucleus and nucleolar type of fluorescence were 32 %, 9 % and 8 % of incidence, respectively. There were more often cytoplasmic (63 %), homogeneous (57 %) and granular (54 %) types of fluorescence in the high-positive ANA titer (> 1/1280) than in the moderate-positive one (1/320–1/640). Nucleolar type of fluorescence (5 children — 8 %) was detected only in the moderate-positive titer. Dots in the nucleus were less common, but in any type of fluorescence (6 children — 9 %). High titers of ANA fluorescence in children were identified in 69 % with an isolated variant of

AIH type 1, while with a combination of AIH and PSC, AIC, multiple autoimmune pathologies high titers were detected in 34 % of children.

Analysis of titers and types of fluorescence with the severity by the degree of liver fibrosis has revealed phase dependence: from fibrosis stage F0 to F2 there is a decrease in the proportion of children with the high-positive ANA titer ($p < 0,001$), and from fibrosis stage F2 to F4 the proportion of patients with the high-positive ANA titer ($p < 0,05$) increases. We have not revealed the dependence of the fluorescence type on the liver fibrosis stage in this sample of patients.

Analysis of ANA content in 16 children during treatment showed that the titer of ANA fluorescence decreased in 10 patients: in 5 of them — became negative (< 1/160), in 4 — the fluorescence titer decreased to the minimum, in 1 — was negative at the onset of treatment and remained the same; in 6 children ANA titer did not change or became higher.

A decrease in the antibody titer in children (10 people — 63 %) was reliably ($p < 0,05$) associated with the reduction in measures of disease activity: ALT — from 43 [20; 156,7] to 19 [12; 50,3]; AST — from 35,7 [27,1; 75,8] to 25,7 [20; 33] and in the relative (from 0,45 [0,2; 0,6] to 0,1 [0,09; 0,11]) and absolute number of immature granulocytes (from 0,03 [0,01; 0,03] to 0,005 [0; 0,01]). However, there was tendency to decreasing CRP, GGT, ALP, WBC, neutrophils, ESR as well as a trend towards increasing albumin, MCHC, RDW-CV.

6 (37 %) children did not experience considerable dynamics in the titer of ANA fluorescence on the background of therapy; there was also a significant reduction during treatment: ALT — from 129,5 [92,3; 333,4] to 30,5 [16,5; 48]; AST —from 148 [74,4; 192,9] to 41,5 [24,4; 55,0], reduced absolute number of immature granulocytes, increased albumin — from 38,1 [36,8; 40,3] to 41 [40,8; 46]. There was tendency to decreased GGT, ALP, WBC, neutrophils, % of immature granulocytes, ESR, increased MCHC, RDW-CV. However, biochemical parameters in this group were significantly higher than in the children with decreased ANA titer.

All the children, who did not experience a decrease in the titer during treatment, had determined liver cirrhosis (F4) on METAVIR scale, the course of the disease was accompanied by the presence of other gastrointestinal diseases: erosive bulbit, gastroduodenitis, erosive gastritis, reflux esophagitis, ulcerative colitis. With remaining ANA titer, the type of fluorescence remained too, new types did not appear.

DISCUSSION

Thus, analysis of the study results shows that ANA have been identified in 85 % children with AIH that exceeds ANA detection in adults (78 %) with AIH [10]. Unlike adult with identified higher ANA titers in case of combined AIH and PBC, no such correlation was found in children with crossed syndrome [6].

It was found that children with AIH often had the following types of ANA fluorescence: cytoplasmic, granular and homogeneous. The comparison of the data obtained on prevailing types of fluorescence in children with AIH is consistent with the data on detected pathognomonic types of ANA fluorescence with AIH in adults obtained by K. L. Raykhelson [6]. The most frequently identified types of fluorescence with AIH are associated, according to the website https://www.anapatterns.org/, with the appearance of antibodies to the cytoplasm, to nucleoprotein and chromatin [11].

It is interesting to note that the proportion of children with the high-positive ANA titer ($p < 0,001$) decreases from fibrosis stage F0 to F2 and increases from fibrosis stage F2 to F4 ($p < 0,05$). The onset of the disease is apparently associated with a more inten-

sive formation of ANA that is confirmed by our data on detecting higher ANA titers in children with AIH in the absence of liver fibrosis (F0). In liver cirrhosis (F4) the proportion of children with high-positive ANA titers is also higher than in F1 — F3. This may be caused by the presence of a genetic predisposition to the disease and requires further study [12].

With a dynamic follow-up of patients during therapy, most children experienced a decrease in ANA titer one year after starting treatment that was associated with clinical efficacy of therapy. This fact is consistent with data, obtained by L.P. Ananyeva, on a decrease in ANA titers against the background of pathogenetic treatment in adults with autoimmune diseases [13].

CONCLUSION

Determination of ANA in children with AIH is of great clinical and diagnostic importance. ANA titer correlates with the severity of the disease. Determination of ANA titer can be used as additional criteria to evaluate efficacy of AIH therapy in children.

REFERENCES/ЛИТЕРАТУРА

1. Klotz W, Herold M. How to test antinuclear antibodies to diagnose autoimmune hepatitis. J Hepatol. 2023 Nov; 79 (5): e206–e207. https://doi.org/10.1016/j.jhep.2023.07.006.
2. Гуменюк ОИ, Голобоков ДО, Малахов ГА, Черненков ЮВ, Сулейманова РР, Волкова ОВ. Аутоиммунный гепатит с исходом в цирроз печени в педиатрической практике. Экспериментальная и клиническая гастроэнтерология. 2020; (1): 126–129. [Gumeniuk OI, Golobokov DO, Malahov GA, Chernenkov YuV, Sulejmanova RR, Volkova OV. A clinical case of autoimmune hepatitis with outcome in cirrhosis of the liver in pediatric practice. Experimental and Clinical Gastroenterology. 2020; (1): 126–129. (In Russ.)] https://doi.org/10.31146/1682-8658-ecg-173-1-126-129.
3. Рекомендации EASL по лечению аутоиммунного гепатита. J of Hepatol. Русское издание. 2015; 63 (5): 111–150. [EASL recommendations for the treatment of autoimmune hepatitis. J of Hepatol. Russian edition. 2015; 63 (5): 111–150. (In Russ.)]
4. Месова АМ, Сексенбаева РЕ. Аутоиммунный гепатит у детей. Вестник Казахского Национального медицинского университета. 2016; 3: 16–19. [Medova AM, Seksenbayeva RE. Autoimmune hepatitis in children. Bulletin of the Kazakhstan National University. 2016; 3: 16–19. (In Russ.)] https://cyberleninka.ru/article/n/autoimmunnyy-gepatit-u-detey-1/viewer.
5. Григорьев КИ, Выхристюк ОФ. Аутоиммунный гепатит у детей. Лечебное дело. 2022; (3–4): 4–13. [Grigoriev KI, Vykhristyuk OF (2022). Autoimmune hepatitis in children. Lechebnoe delo. The Journal of General Medicine. 2022; (3–4): 4–13. (In Russ.)] https://doi.org/10.24412/2071-5315-2022-12913.
6. Райхельсон КЛ, Мительглик УА, Зубарева АС, Дунаева НВ, Булгакова ТВ, Лапин СВ, Барановский АЮ, Тотолян АА. Встречаемость аутоантител у больных с аутоиммунными заболеваниями печени и хроническим гепатитом С. Медицинская иммунология. 2013; 15 (4): 351–360. [Raikhelson KL, Mitelglik UA, Zubareva AS, Dunaeva NV, Bulgakova TV, Lapin SV, Baranovsky AYu, Totolian AA. Incidence of autoantibodies in patients with autoimmune liver diseases and chronic hepatitis C. Medical Immunology. 2013; 15 (4): 351–360. (In Russ.)] https://doi.org/10.15789/1563-0625-2013-4-351-360.
7. Жужула АА, Курбатова ОВ, Сновская МА, и др. Информативность определения антинуклеарных антител при системных поражениях соединительной ткани у детей. Российский иммунологический журнал. 2023; 26 (3): 251–258. [Zhuzhula AA, Kurbatova OV, Snovskaya MA, et al. Significane of determining antinuclear antibodies in systemic connective tissue disorders in children. Russian Journal of Immunology. 2023; 26 (3): 251–258.] https://doi.org/10.46235/1028-7221-9961-SOD.
8. Хроленко ПВ, Дьяконова ЕЮ, Фисенко АП, Сурков АН, Дворяковский ИВ, Яцык СП (2019). Эхографическая характеристика поверхностных структур печени при хронических формах патологии органа у детей. Российский педиатрический журнал. 2019; 22 (6), 338–343. [Khrolenko PV, Dyakonova EYu, Fisenko AP, Surkov AN, Dvoryakovsky IV, Yatsyk SP. Echographic characteristics of the surface structures of the liver in chronic forms of organ pathology in children. Rossiiskiy Pediatricheskiy Zhurnal (Russian Pediatric Journal). 2019; 22 (6): 338–343. (In Russ.).] https://doi.org/10.18821/1560-9561-2019-22-6-338-343.
9. Курбатова ОВ, Мовсисян ГБ, Петричук СВ, Парахина ДВ, Демьянов ДС, Купцова ДГ, Радыгина ТВ, Семикина ЕЛ, Потапов АС, Фрейдлин ЕВ. Информативность лабораторных маркеров в оценке стадии фиброза печени у детей с аутоиммунным гепатитом первого типа. Аллергология и иммунология в педиатрии. 2023; 1: 53–55. [Kurbatova OV, Movsisyan GB, Petrichuk SV, Parakhina DV, Demyanov DS, Kuptsova DG, Radygina TV, Semikina EL, Potapov AS, Freidlin EV. Informative value of laboratory markers in assessing the stage of liver fibrosis in children with type 1 autoimmune hepatitis. Allergology and Immunology in Paediatrics. 2023; (1): 53–55. (In Russ.)] https://doi.org/10.53529/2500-1175-2023-1-53-55.

10. Flikshteyn B, Amer K, Tafesh Z, Pyrsopoulos NT. Diagnosis of Autoimmune Hepatitis. Clin Liver Dis. 2024 Feb; 28 (1): 37–50. https://doi.org/10.1016/j.cld.2023.06.004.
11. https://www.anapatterns.org/
12. Patel D, Salem A, Kania B, Lewis W, Mahmoud A, Alkomos M. Autoimmune hepatitis presenting with concomitant chronic pancreatitis. Radiol Case Rep. 2023 Jun 15; 18 (9): 2871–2875. https://doi.org/10.1016/j.radcr.2023.05.040. PMID: 37359250; PMCID: PMC10285037.
13. Ананьева ЛП, Гарзанова ЛА, Конева ОА, Старовойтова МН, Десинова ОВ, Овсянникова ОБ, Шаяхметова РУ, Черкасова МВ, Алексанкин АП, Насонов ЕЛ. Динамика аутоантител к топоизомеразе I на фоне лечения ритуксимабом у больных системной склеродермией. Научно-практическая ревматология. 2022; 60 (1): 57–63. [Ananyeva LP, Garzanova LA, Koneva OA, Starovoytova MN, Desinova OV, Ovsyannikova OB, Shayakhmetova RU, Cherkasova MV, Aleksankin AP, Nasonov EL. Anti-topoisomerase 1 antibody level changes after B cell depletion therapy in systemic sclerosis. Rheumatology Science and Practice. 2022; 60 (1): 57–63. (In Russ.)] https://doi.org/10.47360/1995-4484-2022-57-63.

Serotype diversity of *Streptococcus pneumoniae* in children with chronic bronchopulmonary pathology in the pre-vaccination and post-vaccination periods

SCO — краткое сообщение

https://doi.org/10.53529/2500-1175-2024-1-41-43

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Keywords: chronic bronchopulmonary pathology, children, *Streptococcus pneumoniae*, serotype, PCV13.

For citation: Komyagina TM, Tryapochkina AS, Alyabieva NM, Lazareva AV, Fisenko AP. Serotype diversity of *Streptococcus pneumoniae* in children with chronic bronchopulmonary pathology in the pre-vaccination and post-vaccination periods. *Allergology and immunology in pediatrics*. 2024; 1: 41-43. https://doi.org/10.53529/2500-1175-2024-1-41-43

Серотиповой состав *Streptococcus pneumoniae* у детей с хронической бронхолегочной патологией в довакцинный и поствакцинный периоды

https://doi.org/10.53529/2500-1175-2024-1-41-43

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Ключевые слова: хроническая бронхолегочная патология, дети, *Streptococcus pneumoniae*, серотип, ПКВ13.

Для цитирования: Комягина ТМ, Тряпочкина АС, Алябьева НМ, Лазарева АВ, Фисенко АП. Серотиповой состав *Streptococcus pneumoniae* у детей с хронической бронхолегочной патологией в довакцинный и поствакцинный периоды. *Аллергология и иммунология в педиатрии*. 2024; 1: 41-43. https://doi.org/10.53529/2500-1175-2024-1-41-43

INTRODUCTION. *Streptococcus pneumoniae* plays an important role in the development of respiratory bacterial infections among children in their early years, people with chronic diseases and elderly people. *Streptococcus pneumoniae* (*S. pneumoniae, pneumococcus*) is the main etiological factor of severe invasive infections (bacteremia, meningitis) and the most common causative agent of acute otitis media, sinusitis as well as community-acquired pneumonia [1]. Nasopharynx epithelium is considered the initial colonization place of *S. pneumoniae* in young children, where it may be detected as a part of the commensal flora [2]. Despite the fact that nasopharyngeal colonization by pneumococcus does not often precede the development of the infectious process, carriage creates source of infection and may be the initial stage of the disease [3].

The main method of fighting pneumococcal infection is vaccinal prevention, which started in the Russian Federation in 2014 using 13-valent pneumococcal conjugate vaccine (PCV13).

It includes serotypes, important for pediatric practice (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18, 19A, 19F, 23F); it is characterized by high immunogenicity and also provides long-lasting immunity and immunological memory [4]. Vaccination causes elimination of vaccine serotypes and an increase in prevalence of non-vaccine, previously rare serotypes among pathogens of invasive infections as well as with carriage of *S. pneumoniae* [5,6].

The problem of pneumococcal infection in children with cystic fibrosis (CF) and congenital bronchial and pulmonary malfunctions (CM) has not been studied enough as *S. pneumoniae* is secreted together with other bacterial pathogens in more than 80 % of cases. However, bacterial infections are generally the leading cause of death just in patients with cystic fibrosis, and bacterial agents might be associated with morbidity and mortality in children with CM [7]. So, understanding the serotype structure of pneumococci and its changes as well as the vaccination effect on serotype strain composition of *S. pneumoniae* with these pathologies is essential determine treatment tactics of these children.

OBJECTIVE of our study: to determine the serotype composition of *Streptococcus pneumoniae* isolates in children with chronic bronchopulmonary pathology prior to mass vaccination against pneumococcal infection and in post-vaccination periods.

MATERIALS AND METHODS.

Over the period of 2011-2021 there was the study of 140 isolates of *S. pneumoniae*, obtained from respiratory specimens (aspirates, bronchial lavage water, sputum) of 86 children (61,4 %) with congenital bronchial and pulmonary malfunctions and 54 children (38,6 %) with cystic fibrosis, observed in FSAI "NMRC for Children's Health" of the Ministry of Health of the Russian Federation. The age of children varied from 0,3 to 17,8 years (the median of 6,5 years). The informed consent of the parents and legal representative was obtained. Demographic and clinical characteristics were examined according to the medical records of patients. Despite the lack of data on the vaccination status of the children screened, official sources for 2015–2018 reports on PCV13 vaccine coverage from 20,9 to 55,3 % of children, born in Moscow [8, 9].

All the isolates were identified using traditional bacteriological methods (colony morphology, α-hemolysis on blood agar, optochin test (Bio-Rad, France) and latex agglutination technique (express test Remel Europe Ltd, UK)).

Pure culture of pneumococci was serotyped in latex agglutination or quelling reactions by Neufeld using specific pool, group and factor serums (Statens Serum Institut, Danmark), and also through molecular typing by multiplex polymerase chain reaction method [10]. Pneumococci were considered untypable if they gave no reaction with any pool serum. *S. Pneumoniae* serotypes, which polysaccharides were included in PCV13, were regarded as "vaccine", all other serotypes were seen as "non-vaccine" (non-PCV13). Statistical data processing was performed using IBM SPSS Statistics 25 software package.

RESULTS AND DISCUSSION. During isolate typing we identified 29 different *S. Pneumoniae* serotypes, two isolates (1,4 %) were assigned to untypable. Most pneumococci (65, %; 91/140) were related to 11 various vaccine serotypes (1, 3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F) in the ten-year study period. The proportion of non-vaccine strains was 35% (49/100) and it was presented by 18 serotypes (6C, 6D, 8, 9N, 10A, 11A, 15B/C, 16F, 20, 22F, 23A, 23B, 28A, 28F, 31, 34, 35C, 35F) as well as two untypable isolates. 19F (22,1 %; 31/140); 3 (11,4%; 16/140); 14 (7,9 %; 11/140) and 23F (7,9 %; 11/140) were leading among vaccine serotypes. 11A serotype (6,4 %; 9/140) prevailed over non-vaccine strains. When considering pre-vaccination (pre-PCV13) and post-vaccination (post-PCV13) periods separately, we revealed the change in the incidence of vaccine and non-vaccine serotypes in time. PCV13 serotypes peaked in 2012, entering pre-vaccination period (2011–2014). This year 27,5 % of specimens have had vaccine serotypes (25/91). It is noteworthy that most of these isolates were obtained from children with CM (68 %; 17/25). 14,19F and 23F (46,9 %; 31/66) were the predominant vaccine serotypes in pre-PCV13-period. These findings are consistent with the results, previously observed in our center for children with the nasopharyngeal carriage of *S. pneumoniae* [6]. Among non-vaccine serotypes 11A (9,1 %; 6/66) occurred more often in children with chronic bronchopulmonary pathology in pre-PCV13-period. However, non-vaccine serotype 15 B/C was most commonly detected in children with the nasopharyngeal carriage [6].

We observed a growing trend in non-vaccine serotypes among children with chronic bronchopulmonary pathology in post-PCV13-period. Their number increased by 4,8 %, and most of the specimens (36,7 %; 18/49) with non-PCV13-serotypes fell on 2016–2017, i.e. right after implementing the vaccine in a wide clinical practice that is consistent with the results of previous studies [6]. It was observed, mainly, in the group of children with CM, who had an increase in the number of strains with non-vaccine serotypes from 32,5 % to 45,7 % after 2014. In addition to increasing number of non-vaccine strains, there was a growth in their serotype variety in the postPCV13-period.

Apart from the identified in the pre-vaccination period (11A, 16F, 6C, 15B/C, 10A, 28A, 35C), 23B, 34, 31, 22F, 28F, 20, 6D, 35F serotypes appeared. Two specimens, related to untypable, were also detected in the post-vaccination period.

CONCLUSIONS. The obtained data prove the impact of PCV on the circulation of vaccine and non-vaccine *S. pneumoniae* strains. An increase in the number and serotype variety of non-vaccine strains after implementing PCV13 in the Russian national immunization programme requires continuous monitoring of *Streptococcus pneumoniae* population. The emergence of strains with new non-vaccine serotypes in children with chronic bronchopulmonary pathology shows the need for further study of pneumococcal population, including their serotype variety and sensitivity to antimicrobial drugs.

REFERENCES/ЛИТЕРАТУРА

1. Лазарева МА, Куличенко ТВ, Алябьева НМ, и др. Носоглоточное носительство Streptococcus pneumoniae у воспитанников детских домов, дошкольных учреждений и неорганизованных детей младше 5 лет. Вопросы современной педиатрии. 2015; 14 (2): 246–255. [Lazareva MA, Kulichenko TV, Alyab'eva NM, et al. Nasopharyngeal carriage of Streptococcus pneumoniae in orphans, preschool children and unorganized children under 5 years. Current Pediatrics. 2015; 14 (2): 246–255. (In Russ.)] https://doi.org/10.15690/vsp.v14i2.1293.
2. Maeda Y, Elborn JS, Parkins MD, et al. Population structure and characterization of viridans group streptococci (VGS) including Streptococcus pneumoniae isolated from adult patients with cystic fibrosis (CF). J Cyst Fibros. 2011 Mar; 10 (2): 133–139. https://doi.org/10.1016/j.jcf.2010.11.003.
3. Протасова ИН, Сидоренко СВ, Фельдблюм ИВ, и др. Эпидемиология серотипов Streptococcus pneumoniae у детей на фоне универсальной вакцинопрофилактики пневмококковой инфекции. Фундаментальная и клиническая медицина. 2021; 6 (4): 54–66. [Protasova IN, Sidorenko SV, Feldblum IV, et al. Epidemiology of Streptococcus pneumoniae serotypes in children before and after pneumococcal vaccination. Fundamental and Clinical Medicine. 2021; 6 (4): 54–66. (In Russ.)] https://doi.org/10.23946/2500-0764-2021-6-4-54-66.
4. Сомова АВ, Романенко ВВ, Голубкова АА. Эпидемиология S. pneumoniae-ассоциированных пневмоний и анализ эффективности вакцинации против пневмококковой инфекции у детей до 6 лет. Эпидемиология и Вакцинопрофилактика. 2018; 17 (1): 25–32. [Somova AV, Romanenko VV, Golubkova AA. Epidemiology of S. pneumoniae-associated pneumonias and the analysis of effectiveness of vaccination against pneumococcal infection in children under the age of six. Epidemiology and Vaccinal Prevention. 2018; 17 (1): 25–32. (In Russ.)] https://doi.org/10.31631/2073-3046-2018-17-1-25-32.
5. Black S. The volatile nature of pneumococcal serotype epidemiology: potential for misinterpretation. Pediatr Infect Dis J. 2010 Apr; 29 (4): 301–303. https://doi.org/10.1097/INF.0b013e3181c391fb.
6. Алябьева НМ, Бржозовская ЕА, Пономаренко ОА, и др. Серотиповой состав Streptococcus pneumoniae, выделенных от детей в Москве до и после внедрения 13-валентной пневмококковой конъюгированной вакцины. Российский педиатрический журнал. 2020; 23 (3): 160–164. [Alyabyeva NM, Brzhozovskaya EA, Ponomarenko OA, et al. Serotype distribution of Streptococcus pneumoniae isolated from children in Moscow before and after introduction of 13-valent pneumococcal conjugate vaccination. Russian pediatric journal. 2020; 23 (3): 160–164. (In Russ.)] https://doi.org/10.18821/1560-9561-2020-23-3-160-164.
7. Ciofu O, Hansen CR, Høiby N. Respiratory bacterial infections in cystic fibrosis. CurrOpinPulm Med. 2013 May; 19 (3): 251–258. https://doi.org/10.1097/MCP.0b013e32835f1afc.
8. Отчет Минздрава России по итогам эпидемического сезонапо ОРВИ и гриппу 2017–2018 гг. Официальный сайт Министерства здравоохранения Российской Федерации.URL: www.rosminzdrav.ru/news/2018/06/01/8132. [The official site of the Ministry of Health of the Russian Federation. URL: www.rosminzdrav.ru/news/2018/06/01/8132. (In Russ.)]
9. Брико НИ. Внедрение массовой пневмококковой вакцинации в России: успехи и проблемы. 3-й Евро-Азиатский саммит специалистов по пневмококковой инфекции. 2019. [Briko NI. Introduction of mass pneumococcal vaccination in Russia: successes and problems. 3rd Euro-Asian summit of specialists inpneumococcal infection. 2019. (In Russ.)]
10. Алябьева НМ, Блинова ТА, Пономаренко ОА, и др. Молекулярное типирование Streptococcus pneumoniae методом мультиплексной полимеразной цепной реакции с учетом распространенности серотипов в Российской Федерации. Вопросы современной педиатрии. 2013; 12 (6): 30–34. [Alyab'eva NM, Blinova TA, Ponomarenko OA, et al. Molecular typing of Streptococcus pneumoniae by the multiplex polymerase chain reaction assay in accordance to the prevalence of serotypes in the Russian Federation. Current Pediatrics. 2013; 12 (6): 30–34. (In Russ.)] https://doi.org/10.15690/vsp.v12i6.871.

Characteristics of subpopulation composition of peripheral blood lymphocytes in children with different forms of congenital ichthyosis

SCO — краткое сообщение

https://doi.org/10.53529/2500-1175-2024-1-44-47

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Keywords: children, ichthyosis, Th17, Treg.

For citation: Kuptsova DG, Murashkin NN, Makarova SG, Ivanov RA, Avetisyan KO, Radigina TV, Kurbatova OV, Petrichuk SV. Characteristics of subpopulation composition of peripheral blood lymphocytes in children with different forms of congenital ichthyosis. *Allergology and immunology in pediatrics*. 2024; 1: 44-47. https://doi.org/10.53529/2500-1175-2024-1-44-47

Характеристика субпопуляционного состава лимфоцитов периферической крови у детей с различными формами врожденного ихтиоза

https://doi.org/10.53529/2500-1175-2024-1-44-47

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Ключевые слова: дети, ихтиоз, Th17, Treg.

Для цитирования: Купцова ДГ, Мурашкин НН, Макарова СГ, Иванов РА, Аветисян КО, Радыгина ТВ, Курбатова ОВ, Петричук СВ. Характеристика субпопуляционного состава лимфоцитов периферической крови у детей с различными формами врожденного ихтиоза. *Аллергология и иммунология в педиатрии*. 2021; 1: 44-47. https://doi.org/ 10.53529/2500-1175-2024-1-44-47

Congenital ichthyosis (CI) is a large heterogeneous group of rare genetic skin diseases with immune disorders and malformation of keratinization of the skin [1]. Defective differentiation of keratinocytes and abnormal formation of the epidermal barrier are observed in these diseases [1, 2]. The resulting dysfunction of the skin barrier causes an increase in transepidermal water loss (TEWL-value of the skin barrier function) and inflammation [3, 4]. Impaired keratinization of the skin regardless of CI form is clinically characterized by dryness, peeling, hyperkeratosis and erythema [1, 2]. Studies in recent years have shown that clinical manifestations of CI and progression of the disease is also caused by uncontrolled activation of immune system cells and inflammatory mediators in the skin [3, 5, 6]. Regarding patients with CI, it was found that a strong activation of cytokines in the IL-17 and TNFα families is closely associated with the severity of the disease and change in TEWL value [7, 8].

CI covers the spectrum of syndromic and non-syndromic dermatosis with a different genetic basis [1,

6]. Non-syndromic ichthyoses include the most described and common phenotype — ichthyosis vulgaris (IV), caused by *FLG* gene mutation (encoding filaggrin). The most prevalent rare non-syndromic CI forms are lamellar ichthyosis (LI, *TGM1* gene mutation, encoding transglutaminase 1 and others) and congenital ichthyosiform erythroderma (CIE; multiple genes), known collectively as autosomal recessive congenital ichthyosis as well as keratinopathic ichthyosis (KPI) with mutations in *KRT1, KRT2* and *KRT10* genes (genes, encoding keratin proteins) [1, 9, 10]. Syndromic forms of CI are characterized by the monogenic type of inheritance, low prevalence and include Netherton syndrome (NS), which is characterized by a large number (> 80) of *SPINK5* gene mutations and specific clinical manifestations [1, 7].

The relevance of the study of the immune system role in developing chronic inflammation with ichthyosis is driven by a search for efficient targeted methods of treating children with various forms of CI. Nowadays, there is still a huge need for safer and more efficient treatment methods of ichthyosis in children [1, 5, 11]. Complex blood immunophenotyping in more patients with ichthyosis will help characterize the immune profile of different disease forms and choose targeted therapy in children with CI.

STUDY OBJECTIVE: to determine value characteristics of major and small lymphocyte populations in children with various forms of congenital ichthyosis.

MATERIALS AND METHODS. 96 children were screened with non-syndromic (n = 65) and syndromic (n = 31) forms of congenital ichthyosis, including Netherton syndrome (NS — group 1, n = 20), X-linked ichthyosis (group 2, n = 11), lamellar ichthyosis (LI — group 3, n = 17), ichthyosiform erythroderma (CIE — group 4, n = 16), keratinopathic ichthyosis (KPI — group 5, n = 15) and ichthyosis vulgaris (IV — group 6, n = 14). The age of the screened children was from 2 months to 18 years. The examination was carried out on the basis of the laboratory of experimental immunology and virology, screening and treatment of patients — in the Department of Dermatology and Allergology of FSAI NMRC for Children's Health" of the Ministry of Health of the Russian Federation. Diagnosis and subtype of CI were made based on the results of molecular genetic studies with NGS.

The study is approved by the local ethics committee (Protocol № 6 of 17.06.2021). Written informed consent was obtained from the children's parents during examination.

All the patients had immunophenotyping of peripheral blood lymphocytes by flow cytometry on «Novocyte» cytofluorimeter (ACEA Biosciences, USA), using monoclonal antibodies (Beckman Coulter, USA). The method of step-by-step gating in $CD45^+$ region determined the composition of: T-lymphocytes ($CD3^+$), T-helpers ($CD3^+CD4^+$), cytotoxic T-lymphocytes ($CD3^+CD8^+$), B- lymphocytes ($CD3^-CD19^+$), NK-cells ($CD^3{-}CD16^+CD56^+$), regulatory T-cells ($CD4^+CD25^{high}CD127^{low}$ — Treg), activated T-helpers ($CD4^+CD25^+CD127^{high}$ — Thact), Th17-lymphocytes ($CD3^+CD4^+CD161^+$ — Th17) and Th2- lymphocytes ($CD3^+CD4^+CD294^+$ — Th2).

Since the study involves children of different age, to assess changes in major and small lymphocyte populations, deviations of individual indicators from the level of the age norm were calculated by the formula:

$X_n = (X_{min} - X) / 0{,}01 \times (X_{max} - X_{min})$, где

X_n — the value of the individual indicator, standardized on the age norm; X — the value of the studied indicator; X_{max} — the upper limit of the age norm; X_{min}— the lower limit of the age norm. The range of the age norm was accepted as 100 %.

Statistical processing of the data obtained was performed using Statistica 10.0 program. Descriptive statistics of quantitative trait is presented in the format: median (lower and upper quartiles) — Me ($Q_{0,25}$– $Q_{0,75}$). The non-parametric Mann-Whitney test was used to evaluate significance of differences between groups. Differences were considered statistically significant at $p < 0{,}05$.

RESULTS AND DISCUSSION

The first stage of the study included analysis of the percentage of major and small lymphocyte populations in children with syndromic and non-syndromic forms of congenital ichthyosis. Regardless of CI form, the children had an increase in the concentration of activated T-helpers relative to the values of the age norm. Analysis revealed a significant increase in the

relative composition of Th17-lymphocytes in the group of children with syndromic forms of the disease as to rates in the group with non-syndromic ones: for the relative composition of Th17 (% from LF) deviation from the norm was 84,3 (30–203) % versus 29,0 (−2,3–77) %, p = 0,005; for the relative composition of Th17 (% from CD4) — 111,8 (22,4–221) % versus 18,2 (−12–80) %, p = 0,001.

Composition analysis of major lymphocyte populations in children with Netherton syndrome, X-linked ichthyosis, lamellar ichthyosis, ichthyosiform erythroderma, keratinopathic ichthyosis and ichthyosis vulgaris showed that the relative and absolute composition of T-lymphocytes, T-helpers, NK-cells, B-lymphocytes was mainly within the age reference values, however, there were statistically significant differences and a large range between the forms of the disease. Patients with Netherton syndrome experienced a reduction in the percentage of cytotoxic T-lymphocytes by 12,5 % (−21–42,6) below the level of the age norm. A similar decrease in the relative composition of $CD8^+$ T-cells was detected in children with lamellar ichthyosis: −10,8 (−27,1–20,7) %. The group of children withc X-linked ichthyosis showed a decline in the relative and absolute composition of B-lymphocytes ($p < 0,05$), and the group with KPI — a decrease in the composition of B-lymphocytes below the age norm. Children with vulgar ichthyosis are characterized by a significant reduction in the composition of NK-cells relative to the age norm and indicators of children with lamellar ichthyosis (p = 0,025) and keratinopathic ichthyosis (p = 0,002).

The greatest changes in the lymphocyte composition were identified in the analysis of small populations of $CD4^+$ T-cells in the peripheral blood in children with different forms of CI. composition content of activated T-helpers by 1,8–3,9 times in regard to the values of the age norm. As for regulatory T-cells, the largest increase in the composition of this population was shown in children with Netherton syndrome and was 126 (46–200) %—for the relative value (% CD4) and 155 (−5–349) % — for the absolute one (cells/ μL). The relative composition of Treg was within normal range in the other groups of children with CI, while the absolute composition of the population was increased in the groups with LI, CIE, KPI и IV. It is worth noting that there was a large spread of Treg content in all forms of congenital ichthyosis.

The content analysis of Th17-lymphocytes in children with different forms of CI showed that the increased population was observed in children with Netherton syndrome: for the relative composition (% CD4) by 112 (65–209) %; for the absolute one (cells/ μL) by 168 (43–342) %. An increase in the absolute number of Th17 was also found in the group of children with ichthyosiform erythroderma and was 190 (76–311) % in regard to the age norm. A rise in the composition of Th2- lymphocytes was revealed with NS, CIE and KPI. The highest growth in the composition of Th2-lymphocytes relative to the values of the age norm was detected in the group of patients with keratinopathic ichthyosis at 200 (131–393) % for the relative composition and at 399 (172–571) % for the absolute one.

Thus, the study has allowed to determine characteristic deviations of the values of major and small lymphocyte populations for different forms of congenital ichthyosis in children. A significant increase in the composition of activated T-helpers and Th17-lymphocytes was shown for pediatric patients with Netherton syndrome, ichthyosiform erythroderma and lamellar ichthyosis, and a rise in the composition of regulatory T-cells — for children with Netherton syndrome, keratinopathic ichthyosis, ichthyosiform erythroderma and ichthyosis vulgaris.

CONCLUSION

The obtained data on the state of cellular immunity in children with different forms of congenital ichthyosis expands the understanding of the disease immunopathogenesis and may serve as a basis for choosing targeted biological therapy and thus allows to improve patients' condition and to predict the course of the disease.

REFERENCES/ЛИТЕРАТУРА

1. Мурашкин НН, Аветисян КО, Иванов РА, Макарова СГ. Врожденный ихтиоз: клинико-генетические характеристики заболевания. Вопросы современной педиатрии. 2022; 21 (5): 362–377. [Murashkin NN, Avetisyan KO, Ivanov RA, Makarova SG. Congenital Ichthyosis: Clinical and Genetic Characteristics of the Disease. Current Pediatrics. 2022; 21 (5): 362–377. (In Russ.)] https://doi.org/10.15690/vsp.v21i5.2459.
2. Тахтарова ТГ, Хисматуллина ЗР, Панова ЛД, Панова АН. Ихтиоз (понятие, патогистология, клиническая картина, лечение). Вестник дерматологии и венерологии. 2021; 97 (3): 6–13. [Takhtarova TG, Khismatullina ZR, Panova LD, Panova AN. Ichthyosis (concept, pathohistology, clinical picture, treatment). Vestnikdermatologiiivenerologii. 2021; 97 (3): 6–13. (In Russ.)] https://doi.org/10.25208/vdv1214.
3. Аветисян КО, Мурашкин НН, Макарова СГ, Петричук СС, Купцова ДГ. Особенности клеточного иммунитета у детей с врожденным ихтиозом и их роль в стратегии патогенетической терапии заболевания. Вопросы современной педиатрии. 2023; 22 (5): 415–424. [Avetisyan KO, Murashkin NN, Makarova SG, Petrichuk SS, Kuptsova DG. Features of Cell-Mediated Immunity in Children with Congenital Ichthyosis and Their Role in the Pathogenetic Management. Current Pediatrics. 2023; 22 (5): 415–424. (In Russ.)] https://doi.org/10.15690/vsp.v22i5.2645.
4. Vahlquist A, Törmä H. Ichthyosis: A Road Model for Skin Research. Acta Derm Venereol. 2020; 100 (7): adv00097. Published 2020 Mar 25. https://doi.org/10.2340/00015555-3433.
5. Lefferdink R, Rangel SM, Chima M, et al. Secukinumab responses vary across the spectrum of congenital ichthyosis in adults. Arch Dermatol Res. 2023; 315 (2): 305–315. https://doi.org/10.1007/s00403-022-02325-3.
6. Еремина АА, Герлингер АВ, Макеенко ОА, Кох НВ, Сергеева ИГ. Внедрение современных генетических и инструментальных методов обследования в ведении пациентов с вульгарным ихтиозом и атопическим дерматитом. Клиническая дерматология и венерология. 2023; 22 (4): 399–405. [Eremina AA, Gerlinger AV, Makeenko OA, Kokh NV, Sergeeva IG. Introduction of modern genetic and instrumental examination methods in patients with ichthyosis vulgaris and atopic dermatitis. Klinicheskaya Dermatologiya i Venerologiya. 2023; 22 (4): 399–405. (In Russ.)] https://doi.org/10.17116/klinderma202322041399.
7. Czarnowicki T, He H, Leonard A, et al. The Major Orphan Forms of Ichthyosis Are Characterized by Systemic T-Cell Activation and Th-17/Tc-17/Th-22/Tc-22 Polarization in Blood. J Invest Dermatol. 2018; 138 (10): 2157–2167. https://doi.org/10.1016/j.jid.2018.03.1523.
8. Paller AS, Renert-Yuval Y, Suprun M, et al. An IL-17-dominant immune profile is shared across the major orphan forms of ichthyosis. J Allergy Clin Immunol. 2017; 139 (1): 152–165. https://doi.org/10.1016/j.jaci.2016.07.019.
9. Новиков ЮА, Зыкова ЕА, Правдина ОВ. Описание клинического случая врожденной ихтиозиформной эритродермии Брока. Вестник дерматологии и венерологии. 2019; 95 (3): 46–53. [Novikov Yu A, Zykova E A, Pravdina OV. Clinical case of Brock's congenital ichthyosiform erythroderma. Vestnik Dermatologii i Venerologii. 2019; 95 (3): 46–53. (In Russ.)] https://doi.org/10.25208/0042-4609-2019-95-3-46-53.
10. Кошкин СВ, Чермных ТВ, Евсеева АЛ, Рябова ВВ, Рябов АН. Ламеллярный врожденный ихтиоз. Вестник дерматологии и венерологии. 2016; 92 (5): 44–50. [Koshkin SV, Chermnykh TV, Evseeva AL, Ryabova VV, Ryabov AN. Lamellar congenital ichthyosis in practice of dermatologists. Vestnik dermatologii i venerologii. 2016; 92 (5): 44–50. (In Russ.)] https://doi.org/10.25208/0042-4609-2016-92-5-44-50.
11. Петрова СЮ, Альбанова ВИ, Ноздрин КВ, Гузев КС. Основные эффекты воздействия ретинола пальмитата на структуры кожи и принципы его применения в дерматологической практике. Вестник дерматологии и венерологии. 2023; 99 (1): 6–17. [Petrova SY, Albanova VI, Nozdrin KV, Guzev KS. Main effects of retinol palmitate on skin structures and the technology of its use in dermatological practice. Vestnik dermatologii i venerologii. 2023; 99 (1): 6–17. (In Russ.)] https://doi.org/10.25208/vdv1375.

Antinuclear antibodies in children with Wilson's disease

SCO — краткое сообщение

https://doi.org/10.53529/2500-1175-2024-1-48-52

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Keywords: children, Wilson's disease, liver fibrosis, Th17 lymphocytes, antinuclear factor, Hep-2, autoimmunity, cytokines, molecular genetic study.

For citation: Kurbatova OV, Zhuzhula AA, Lapin SV, Snovskaya MA, Kozlova DI, Petrichuk SV, Kuptsova DG, Kuznetsova DA, Movsisyan GB, Komarova AD, Radygina TV, Guslev AB, Kholopova IV, Semikina EL, Makarova SG, Potapov AS, Fisenko AP. Antinuclear antibodies in children with Wilson's disease. *Allergology and immunology in pediatrics.* 2024; 1: 48-52. https://doi.org/10.53529/2500-1175-2024-1-48-52

Антинуклеарные антитела у детей с болезнью Вильсона

https://doi.org/10.53529/2500-1175-2024-1-48-52

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Ключевые слова: дети, болезнь Вильсона, фиброз печени, Th17-лимфоциты, антинуклеарный фактор, Hep-2, аутоиммунитет, цитокины, молекулярно-генетическое исследование.

Для цитирования: Курбатова ОВ, Жужула АА, Лапин СВ, Сновская МА, Козлова ДИ, Петричук СВ, Купцова ДГ, Кузнецова ДА, Мовсисян ГБ, Комарова АД, Радыгина ТВ, Гуслев АБ, Холопова ИВ, Семикина ЕЛ, Макарова СГ, Потапов АС, Фисенко АП. Антинуклеарные антитела у детей с болезнью Вильсона. *Аллергология и иммунология в педиатрии.* 2024; 1: 48-52. https://doi.org/10.53529/2500-1175-2024-1-48-52

ВВЕДЕНИЕ

Wilson-Konovalov's disease (WD) is a hereditary condition, transmitted as an autosomal recessive trait and associated with impaired excretion of cooper from the body. Excessive accumulation of cooper causes combined lesion of parenchymal organs (primarily liver) and brain [1, 2]. There is a description of over 700 *ATP7B* protein mutations (Cu^{++} transporting beta polypeptide; beta-polypeptide cooper-transporting ATPase), which may cause cooper metabolism disorder [1, 2, 3]. Missense variant is the most prevalent pathogenic variant, leading to replacement

of histidine by glutamine in 1069 position of the encoded protein *c.3207C>A (p.H1069Q)* [4]. It is also found that this H1069Q variant is associated with late neurological manifestations [5].

The clinical picture of Wilson's disease is distinguished by the polymorphism: in 40–45 % of cases the disease debuts with liver damage, developing at the age 5–18; rarer (in 30 %) — with the development of neurological and psychiatric disorders [6]. The symptoms of the disease include: jaundice, edema of shin, increased abdominal volume, esophageal varicose veins, propensity to form bruising and extended hemorrhage. Some patients with WD may have only minor abnormalities in biochemical parameters of liver function with no other symptoms over the years. Other patients with WD experience a fast progression of liver inflammation in the form of chronic hepatitis with high activity, pronounced jaundice, necrosis of hepatocytes and rapid transformation into cirrhosis [6]. Considering diversity of clinical symptoms, there are difficulties in differential diagnosis of Wilson's disease with other liver diseases [7]. In the early stages of hepatocellular damage, the involvement of endoplasmic reticulum, mitochondria, peroxisome and nucleoli in the process, combined with decreased activity of mitochondrial enzymes causes lipid peroxidation, the accumulation of triglycerides, and further — necrosis of hepatocytes. Malondialdehyde, produced by lipid peroxidation, stimulates collagen synthesis, contributing to fibrogenesis [8].

There is the description of disturbances in the immune system in patients with WD, progressing with increasing liver fibrosis stage and age of patients [9]. Subpopulation composition of lymphocytes in children with WD changes and is characterized by involvement of T-cellular immunity in the process of liver fibrosis, and changes are similar to those in other liver diseases [10]. For instance, different stages of fibrosis in non-alcoholic fat liver are accompanied by the accumulation of T-cell and NK-cell subpopulations with different functions and phenotypes in the liver tissues that usually causes pro-inflammatory effects [11].

The process of liver fibrosis is accompanied by changes in the profile of circulating cytokines in chronic liver disease, by the concentration of which it is possible to carry out differential diagnostics between fibrosis stages [12, 13].

The clinical picture of chronic inflammation of the liver in WD is less distinguishable from liver damage of another genesis and causes the development of liver cirrhosis without pathogenetic therapy. This points to the need for detecting WD in all patients with chronic damage of hepatic parenchyma [14].

Characteristic of chronic hepatitis in WD is a moderate increase in biochemical markers of cytolysis, cholestasis and bilirubin exchange with a high level of structural changes in hepatic parenchyma on the results of morphological examination of liver biopsy slides [15].

Clinically WD may occur like autoimmune hepatitis with a detected high level of serum immunoglobulins and nonspecific autoantibodies. Hence, it is also necessary to exclude Wilson's disease in patients with autoimmune hepatitis with inefficiency of corticosteroid therapy [15]. However, the detection rate of autoantibodies in WD has not been studies, only isolated cases of their detection are described that often causes a false positive diagnosis of "autoimmune hepatitis" [16].

STUDY OBJECTIVE: to evaluate the presence of antinuclear antibodies, parameters of cellular immunity and the composition of circulating cytokines in children with WD.

MATERIALS AND METHODS. As part of diagnostic measures for screening children with liver diseases, treated in FSAI "NMRC for Children's Health" of the Ministry of Health of the Russian Federation, there was examination of 46 children with clinical signs of autoimmune hepatitis. All the children got evaluation of the liver fibrosis stage by the method of transient liver elastography on FibroScan F502 (EchoSence, France). METAVIR scale was used to diagnose LF stage [17]. Complete blood test (automated hematologic Sysmex XN 550, Japan), biochemical blood test (AU680, USA), immunophenotyping of peripheral blood lymphocytes (CYTOMICS FC500, Beckman Coulter, USA), the determination of antinuclear antibody (ANA) on the cell line HEp-2 using the reaction of indirect immunofluorescence (RNIF, Immco Diagnostics, Inc, USA). Determining the level of circulating cytokines was performed using enzyme-linked immunosorbent assay MILLIPLEX Human Cytokine, based on Luminex technology (Merck Millipore, Germany). To confirm Wilson's disease, molecular genetic study was carried out by the Sanger method of sequencing on 3500xL Genetic Analyzer (Applied Biosystems, USA). All changes in the reference AT-

P7B gene sequence were described according to the HGVS nomenclature in accordance with the accepted recommendations [18]. Statistical calculations were carried out using Statistica 10.0 program (USA).

RESULTS AND DISCUSSION

Out of 46 examined children, 11 (24 %) were diagnosed with "Wilson's disease", based on molecular genetic testing. The following pathogenic variants of ATP7B gene were identified, causing the development of WD: *c.2304dup (p.M769HfsTer26), c.2998G>A (p.G1000R), c.3002T>G (p.V1001G), c.3036dup (p.K1013QfsTer15), c.3472_3482del (p.G1158FfsTer2)* и *c.3207C>A (p.H1069Q). The variant c.3207>A (H1069Q)* was more common as a part of compound-heterozygous mutation in the presented sample of patients, and as a part of homozygous mutation only in two children. 35 children (76%) got verified diagnosis of "autoimmune hepatitis".

ANA on the cell line HEp-2 were found in 4 out of 11 children with WD diagnosis, using RNIF, moreover, 3 children had a low titer of ANA (1/160), one patient had a high one (1/2560). Only the facts of low ANA titers in patients with WD were previously reported [15]. The type of fluorescence in all children with WD was similar— nuclear granular (AC-2,4). It is interesting to note that only in one child with revealed ANA, the pathogenic variant *c.3207>A (H1069Q)* was in homozygous state. *H1069Q* mutation in the homozygous state causes the development of severe hepatic insufficiency, depression, dysarthria and tremor at an earlier age that a mutation in the compound-heterozygous state [5, 19].

According to transient liver elastography, the child with a high ANA titer (1/2560) did not have liver fibrosis of F0 stage. Perhaps such a high ANA titer of the child is associated with sensitization to cow's milk protein (class 3), egg (class 2), wheat (class 3), total gE = 3043 IU/mL. In children with low ANA titer liver fibrosis ranged from F0 to F2. Hence, the presence of ANA in children with WD did not depend on liver fibrosis stage in this sample of patients.

The comparison of laboratory values of children with WD and the presence of ANA with no antibodies revealed that the former had a significantly lower concentration of albumin in serum than the latter: Me = 65,3 [63,55; 66,85] g/l versus Me = 68 [67; 69,3] g/l (p = 0,042).

Children with WD are characterized by increased concentration of T-cells through the population of T-helpers with a decrease in cytotoxic T-lymphocytes, B-lymphocytes and NK-cells against the backdrop of a rise in Thact, Th17-lymphocytes and Treg [20]. The level of Treg, Th17-lymphocytes, activated T-helpers in the group of children with and without ANA did not have statistical difference and was characterized by a large data range, especially in the group of children without ANA. Nevertheless, we can note tend to decrease the relative amount of Treg and to increase the relative amount of Th17-lymphocytes in the group of children with ANA. Perhaps a large spread of parameters of cellular immunity is due to the fact that the group of children without ANA had children with different fibrosis stages, including F3-4 stage, in which the level of Th17-lymphocytes is significantly higher than in the early stages of liver fibrosis in children with WB [9].

The evaluation of the level of circulating cytokines revealed that the level of IL27 was much higher in the group of children with ANA than in the one without ANA: Me = 12097 [11028; 13299] pg/ml versus

Me = 8338 [8,8; 10559] pg/ml (p = 0,024). Yet, IL22 and TNFα were significantly lower than in the group without ANA and were: TNFα — Me = 60 [53,55; 64,86] pg/ml versus Me = 130 [66,6; 164,5] pg/ml (p = 0,024); IL22 — Me = 20,3 [16,4; 22,4] pg/ml versus Me=41,9 [34,8; 592,9] pg/ml (p=0,012). In addition, there was tend to a higher concentration of IL4 and IL9 in children with ANA. It is worth noting a large spread in values of circulating cytokine levels that might also be associated with the fact that

the children with WD in this sample experienced different liver fibrosis stages, and the change in the cytokine profile of patients is related to liver fibrosis stages [12, 13].

The detection of antinuclear antibodies in patients with accumulation diseases is justified in terms of pathophysiology: damaged tissues of the body, including those associated with reactions to accumulating toxic components, are capable of inducing immune response to tissue damage. Liver damage as well as in Wilson's disease, can be a prime example of such reactions due to the fact that there is a considerable number of lymphocytes and macrophages in the liver tissue, which are the main producers of cytokines. Hence, assessment and monitoring of immune responses in WD is a promising marker of the severity of the condition and therapy efficacy. A promising area of research is broadening methods of drug therapy, with the inclusion of immunomodulators, metabolites and antioxidants, optimizing immune responses and the cytokine profile of patients [21].

CONCLUSION

The presence of ANA in children with Wilson's disease may indicate the attachment of an autoimmune component to the congenital genetic disease. A larger study is required regarding the frequency of ANA disclosure in children with WD, the association of ANA with liver fibrosis and the presence of specific pathogenic variants in *ATP7B* gene.

REFERENCES/ЛИТЕРАТУРА

1. Фисенко АП, Сурков АН, Потапов АС. Болезнь Вильсона у детей. М: НМИЦ здоровья детей, 2019. — С. 84 [Fisenko AP, Surkov AN, Potapov AS. Wilson's disease in children. M: National Medical Research Center for Children's Health, 2019. — P. 84. (In Russ.)]
2. Lucena-Valera A, Ruz-Zafra P, Ampuero J. Wilson's disease: overview. Enfermedad de Wilson. Med Clin (Barc). 2023; 160 (6): 261–267. https://doi.org/10.1016/j.medcli.2022.12.016.
3. Lu ZK et al. Phenotypes and ATP7B gene variants in 316 children with Wilson disease. Zhonghua Er Ke Za Zhi. 2022; 60 (4): 317–322. https://doi.org/10.3760/cma.j.cn112140-20210827-00708.
4. Баязутдинова ГМ, Щагина ОА, Поляков АВ. Мутация с.3207C>A гена ATP7B — наиболее частая причина гепатолентикулярной дегенерации в России: частота и причина распространения. Медицинская генетика. 2018; 17 (4): 25–30. [Baiazutdinova GM, Shchagina OA, Poliakov AV. The study of common mutation p.H1069Q in ATP7B gene in Russian WD-patients. Medical Genetics. 2018; 17 (4): 25–30. (In Russ.)] https://doi.org/10.25557/2073-7998.2018.04.25-30.
5. Постригань АЕ, Жалсанова ИЖ, Фонова ЕА, Скрябин НА. Гены-модификаторы как причина клинического полиморфизма болезни Вильсона — Коновалова. Генетика. 2021; 57 (5): 516–527. [Postrigan AE, Zhalsanova IZh, Fonova EA, Skryabin NA. Modifier genes as the cause of clinical polymorphism of Wilson — Konovalov disease. Genetics. 2021; 57 (5): 516–527. (In Russ.)] https://doi.org/10.31857/S001667582105009X.
6. Циммерман ЯС. Болезнь Вильсона — гепатоцеребральная дистрофия. Клиническая медицина. 2017; 4: 310–315. [Zimmerman JS. Wilson's disease — hepatocerebral dystrophy. Clinical medicine. 2017; 4: 310–315. (In Russ.)] http://dx.doi.org/10.18821/0023-2149-2017-95-4-310-315.
7. Идрисова СШ, Шаймарданова ГМ, Тулеева АИ, Абдраимова СО, Кузембаева КУ. Трудности диагностики болезни Коновалова — Вильсона. Клиническая медицина Казахстана. 2014; 4 (34): 70–74. [Idrisova SSH, Shaimardanova GM, Tuleeva AI, Abdraimova SO, Kuzembaeva KU. Difficulties in diagnosing Konovalov — Wilson disease. Clinical Medicine of Kazakhstan. 2014; 4 (34): 70–74. (In Russ.)] URL: https://cyberleninka.ru/article/n/trudnosti-diagnostiki-bolezni-konovalova-vilsona.
8. Scheiber IF, Brůha R, Dušek P. Pathogenesis of Wilson disease. Handb Clin Neurol. 2017; 142: 43–55. https://doi.org/10.1016/B978-0-444-63625-6.00005-7.
9. Курбатова ОВ, Купцова ДГ, Безрукавникова ЛМ, Радыгина ТВ, Мовсисян ГБ, Анушенко АО, Комарова АД, Потапов АС, Петричук СВ, Фисенко АП. Особенности иммунного статуса у детей с болезнью Вильсона — Коновалова при разных стадиях фиброза печени. Российский иммунологический журнал. 2022; 25 (4): 453–460. [Kurbatova OV, Kuptsova DG, Bezrukavnikova LM, Radygina TV, Movsisyan GB, Anushenko AO, Komarova AD, Potapov AS, Petrichuk SV, Fisenko AP. Features of the immune status in children with Wilson — Konovalov disease at different stages of liver fibrosis. Russian Immunological Journal. 2022; 25 (4): 453–460. (In Russ.)] https://doi.org/10.46235/1028-7221-1193-FOI,КМКВ, вып. 2, с. 5–11.
10. Курбатова ОВ, Петричук СВ, Мовсисян ГБ, Купцова ДГ, Радыгина ТВ, Анушенко АО, Семикина ЕЛ, Потапов АС. Роль малых популяций лимфоцитов при формировании фиброза печени у детей с гликогеновой болезнью. Российский иммуноло-

гический журнал. 2023; 26 (3): 337–344. [Kurbatova OV, Petrichuk SV, Movsisyan GB, Kuptsova DG, Radygina TV, Anushenko AO, Semikina EL, Potapov AS. The role of small populations of lymphocytes in the formation of liver fibrosis in children with glycogen storage disease. Russian Immunological Journal. 2023; 26 (3): 337–344. (In Russ.)] https://doi.org/10.46235/1028-7221-10013-ROM.

11. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. Cells. 2020; 9 (4): 875. https://doi.org/10.3390/cells9040875.
12. Курбатова О, Закиров Р, Сурков А, Никитин А, Самохина И, Фрейдлин Е, Потапов А, Петричук С. Уровень сывороточных цитокинов при разных стадиях фиброза печени у детей с печеночными формами гликогеновой болезни. Клиническая лабораторная диагностика. 2016; 61 (9): 537. [Kurbatova O, Zakirov R, Surkov A, Nikitin A, Samokhina I, Freidlin E, Potapov A, Petrichuk S, Level of serum cytokines at different stages of liver fibrosis in children with hepatic forms of glycogen storage disease. Clinical laboratory diagnostics. 2016; 61 (9): 537. (In Russ.)]
13. Kirchmeyer M, Gaigneaux A, Servais FA, Arslanow A, Casper M, Krawczyk M, Lammert F, Behrmann I. Altered profiles of circulating cytokines in chronic liver diseases (NAFLD/HCC): Impact of the PNPLA3I148M risk allele. Hepatol Commun. 2023 Nov 22; 7 (12): e0306. https://doi.org/10.1097/HC9.0000000000000306. PMID: 38015590; PMCID: PMC10667005.
14. Socha P, Janczyk W, Dhawan A et al. Wilson's Disease in Children: A Position Paperby the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Feb; 66 (2): 334–344. https://doi.org/10.1097/MPG.0000000000001787.
15. Клинические рекомендации. URL: https://cr.minzdrav.gov.ru/schema/376_2. [Clinical recommendations, URL: https://cr.minzdrav.gov.ru/schema/376_2. (In Russ.)]
16. Ерёмина ЕЮ. Болезнь Вильсона — Коновалова. Вестник современной клинической медицины. 2011; 1: 38–46. [Eremina EYu. Wilson — Konovalov disease. Bulletin of modern clinical medicine. 2011; 1: 38–46. (In Russ.)]
17. Кулебина ЕА, Сурков АН, Куликов КА, Потапов АС, Бессонов ЕЕ. Валидация показателей транзиентной эластографии для оценки стадии фиброза печени у детей. Лечащий Врач. 2020; 8: 57–60. [Kulebina EA, Surkov AN, Kulikov KA, Potapov AS, Bessonov EE. Validation of transient elastography indicators for assessing the stage of liver fibrosis in children. Treating Doctor. 2020; 8: 57–60. (In Russ.)]. https://doi.org/10.26295/OS.2020.26.84.00.
18. den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, Roux AF, Smith T, Antonarakis SE, Taschner PE. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat. 2016 Jun; 37 (6): 564–569. https://doi.org/10.1002/humu.22981.
19. Członkowska A, Gromadzka G, Chabik G. Monozygotic female twins discordant for phenotype of Wilson's disease. Mov Disord. 2009 May 15; 24 (7): 1066–1069. https://doi.org/10.1002/mds.22474.
20. Курбатова ОВ, Петричук СВ, Купцова ДГ, Радыгина ТВ, Семикина ЕЛ, Потапов АС. Возрастные особенности субпопуляционного состава и метаболизма лимфоцитов у детей с болезнью Вильсона — Коновалова. Кремлевская медицина. Клинический вестник. 2023 Июнь; 2: 5–11. [Kurbatova OV, Petrichuk SV, Kuptsova DG, Radygina TV, Semikina EL, Potapov AS. Age-related features of the subpopulation composition and metabolism of lymphocytes in children with Wilson — Konovalov disease. Kremlin Medicine Clinical Bulletin. 2023 Jun; 2: 5–11. (In Russ.)] https://doi.org/10.48612/cgma/a5rx-evxd-xkk9.
21. Сандлер ЮГ, Матвеева ЮА, Винницкая ЕВ, Гендриксон ЛН, Кейян ВА. Возможности применения антигипоксантной и антиоксидантной терапии при неалкогольной болезни печени, РМЖ. Медицинское обозрение. 2016; 24 (26): 1815–1818. [Sandler YuG, Matveeva YuA, Vinnitskaya EV, Gendrikson LN, Keyan VA. Possibilities of using antihypoxic and antioxidant therapy for non-alcoholic liver disease, Breast Cancer. Medical Review. 2016; 24 (26): 1815–1818. (In Russ.)] https://www.rmj.ru/articles/gastroenterologiya/Vozmoghnosti_primeneniya_antigipoksantnoy_i_antioksidantnoy_terapii_pri_nealkogolynoy_bolezni_pecheni/#ixzz8L5e5zMkT.

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В ПЕДИАТРИИ
ALLERGOLOGY AND IMMUNOLOGY
IN PEDIATRICS