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UNSOLVED PROBLEMS OF FOOD ALLERGY IN CHILDREN

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Abstract. ***Introduction.*** The article discusses the most significant problems faced by a pediatrician, family medicine physician, and allergist-immunologist when caring for children with food allergy (FA). Unsolved problems of FA still include the heterogeneity of information about its prevalence and age dynamics. The clinical value of various examination methods are discussed, revealing the main common errors in the interpretation of tests. Cases of unjustified prescription of elimination diets in children with unproven PA are considered. We present our own data obtained during observation of cohorts of pediatric patients in the city allergology office of St. Petersburg. Among 263 children diagnosed with bronchial asthma, in 91 cases (34.6%) positive (>0.35 IU/ml) specific IgE was found in the blood serum to food products (in descending order of frequency): chicken egg white, milk, cod, wheat, soy, oats. The development of respiratory symptoms when consuming certain products was recorded in 16 people (6.1% of the sample). The paper provides clinical characteristics of this small subgroup of children with bronchial asthma who are indicated for an individually selected elimination diet. The advantages and disadvantages of a promising method of treating FA — oral immunotherapy with food allergen — are considered. The method provides protection against the development of a severe and life-threatening episode if the patient accidentally consumes food allergen. The advantages and disadvantages of the most popular strategies in the prevention of FA in children, starting from the prenatal period, including the use of hydrolyzed formulas and the introduction of potentially allergenic products into complementary foods, were assessed. ***Conclusion.*** In the field of prevention, diagnosis and treatment of food allergies in children at the present stage, there are significant unresolved problems. The development and approval of recommendations for conducting food challenge tests is required. Interpretation of tests can only be carried out in direct connection with knowledge of the history and clinical picture of the disease in the child. The problem of food allergies continues to focus the efforts of both the international community and domestic scientists.

Keywords: *children, food allergy, diet therapy, prevention, clinical manifestations of food allergy*

НЕРЕШЕННЫЕ ПРОБЛЕМЫ ПИЩЕВОЙ АЛЛЕРГИИ У ДЕТЕЙ

© Ольга Валерьевна Трусова, Андрей Вячеславович Камаев

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Резюме. ***Введение.*** В статье рассмотрены наиболее значимые проблемы, с которыми сталкивается педиатр, врач семейной медицины, аллерголог-иммунолог при ведении детей с жалобами на пищевую аллергию (ПА). К нерешенным проблемам ПА по-прежнему относят разнородность сведений о ее распространенности и возрастной динамике. Обсуждается информативность и клиническая ценность различных

методов обследования, с раскрытием основных типичных ошибок при интерпретации анализов. Рассмотрены случаи необоснованного назначения элиминационных диет у детей при недоказанной ПА. Приведены собственные данные, полученные при наблюдении когорт пациентов детского возраста в городском аллергологическом кабинете Санкт-Петербурга. У 263 детей с диагнозом «бронхиальная астма» в 91 случае (34,6%) обнаруживали положительные (>0,35 МЕ/мл) специфические IgE в сыворотке крови к пищевым продуктам (в порядке убывания частоты): белок куриного яйца, молоко, треска, пшеница, соя, овес. Развитие респираторных симптомов при употреблении определенных продуктов фиксировали у 16 человек (6,1% выборки). В работе дана клиническая характеристика этой небольшой подгруппы детей с бронхиальной астмой, которым показана индивидуально подобранная элиминационная диета. Рассмотрены преимущества и недостатки перспективного метода лечения ПА — оральной иммунотерапии с пищевым аллергеном. Метод дает защиту от развития тяжелого и жизнеугрожающего эпизода при случайном употреблении пищевого аллергена пациентом. Оценены преимущества и недостатки наиболее популярных стратегий в профилактике ПА у детей, начиная с внутриутробного периода, в том числе, применение профилактических гидролизных смесей, введение потенциально аллергенных продуктов в прикорм. ***Заключение.*** В области профилактики, диагностики и лечения пищевой аллергии у детей на современном этапе существуют значимые нерешенные проблемы. Требуется разработка и утверждение рекомендаций по проведению провокационных пищевых проб. Интерпретацию анализов можно проводить только в непосредственной связи со знанием анамнеза и клинической картины заболевания у ребенка. Проблема пищевой аллергии продолжает концентрировать усилия и мирового сообщества, и отечественных ученых.

Ключевые слова: *дети, пищевая аллергия, диетотерапия, профилактика, клинические проявления пищевой аллергии*

INTRODUCTION

Food allergy (FA) is a food-induced pathological reaction based on immune mechanisms [1]. The immune mechanisms of allergic reaction are mediated by specific immunoglobulins E (IgE-mediated reactions) or have a cellular mechanism (non-IgE-mediated) [2]. Several mechanisms may be involved in the pathogenesis of FA-associated disease (so-called mixed-type reactions), but allergen-specific IgG of any subclass (including IgG4) is not clinically relevant in any of the described FA-associated conditions [1]. The term "food hypersensitivity" does not show anything about the mechanisms of pathogenesis of reactions to some food, so its application to immunologically determined reactions to food is inappropriate [1]. However, a clear distinction should be made between cases of "food intolerance" in which, despite the certain association of clinical manifestations with food intake, there is no reproducibility and consistency of the reaction or any immunologic mechanisms [1, 3].

HOW COMMON IS FOOD ALLERGY IN CHILDREN?

The overall prevalence of FA is thought to be increasing everywhere, and the spectrum of its clinical manifestations is also expanding [4]. A meta-analysis of 23 studies conducted between 2000 and 2012 in Europe showed that the frequency of FA found in patient at any time during his or her life was 17.3% according to questionnaire data. The prevalence of sensitization by detection of specific IgE (sIgE) to food was 10.1%, proportion of patients with positive allergy skin tests (AST) with food was 2.7%, and probability of a positive result of provocative test for food allergy diagnosis (PT) was only 0.9%. At the same time, significant regional differences in the incidence of FA were noted [5]. Data revision was done in 2023 and linked the results of studies conducted between 2000 and 2021 in all European countries, including the Russian Federation and Turkey, showed an increase in the prevalence of FA, using a questionnaire, and the detection of sensitization. The prevalence of FA noted ever in life was 19.9%, according to questionnaire data, the frequency of laboratory-detected sensitization (sIgE) to food increased to 16.6%; a proportion of positive ASTs to food increased to 5.7%, and the probability of receiving a positive PT did not change significantly, only 0.8% [6]. Thus, the "incidence of FA" has significant differences depending on how it is confirmed. The detection of food sensitization by AST and sIgE has increased over the last decades, possibly reflecting a true increase in FA, but may also be a consequence of the increased vigilance and coverage of allergy screening methods in different countries and general increase in the number of studies on FA. The most recent and comprehensive meta-analysis suggests that large, well-coordinated studies of rigorous de-

sign, including mandatory confirmation of the diagnosis by double-blind, placebo-controlled PT, are needed to more accurately determine the incidence of PA [6].

WHICH FOOD IS THE MOST ALLERGENIC?

At first, the concept of the "Big Eight" (a list of foods that are the most common causes of FA) was proposed in 2014 by the European Academy of Allergy and Clinical Immunology (EAACI) based on research data conducted in 2000–2012. According to current clinical recommendations, the Russian "Big Eight" foods that most often is the cause of allergic reactions include cow milk proteins (CMP), chicken eggs, peanuts, nuts, fish, seafood, wheat and soy [1]. A review and meta-analysis of publications from 2000 to 2021 (total number of studies — 93) showed that the "Big Eight" has not changed during this time [6]. Data from the meta-analysis on the frequency of FAs for G8 foods are presented in Figure 1.

In the study of the sensitization spectrum in children, who lived in Ekaterinburg, aged from

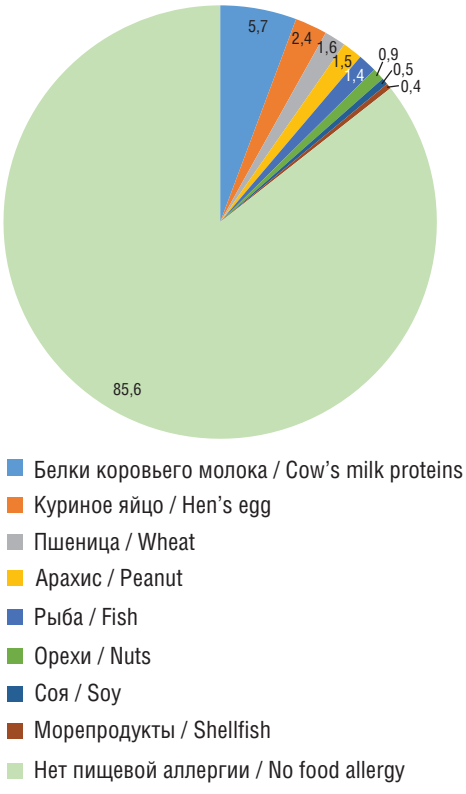

Fig. 1. The prevalence of food allergies according to research data [6]

Рис. 1. Распространенность видов пищевой аллергии в популяции по данным [6]

4 months to 16 years and had anaphylaxis due to allergic reaction to food, causative allergens were identified in 100% of cases. CMP (51.67%), various types of nuts (33%), egg (16.67%), walnuts (16.67%), fish (15%), kiwi (11.67%), peanuts (11.67%) were the leading causes of anaphylaxis. Children who suffered anaphylaxis due to allergic reaction to food were also sensitized to non-food allergens: birch pollen (68.33%), cat fur (40.0%), dog fur (16.6%), and grass pollen (13.3%) [7].

DOES THE AGE OF A PATIENT MATTER

The frequency of allergies to various foods changes with age. Moreover, for the most important and allergenic products, positive dynamics are expected in the form of the formation of tolerance or "outgrowing" allergies. In many cases, this is exactly what happens, and the child begins to tolerate foods such as cow milk, chicken eggs, and wheat without developing a reaction. It is known that the most significant food allergen in young children, CMP, causes allergic reactions in 2–3% of infants, and by the age of 5, approximately 80% of patients develop tolerance. Therefore, the prevalence of FA to CMP allergens at the age of 6 years decreases and is less than 1% [1].

ARE THERE ANY METHODS FOR TREATMENT OF SEVERE FOOD ALLERGY?

In case of confirmed severe FA, patients are forced to strictly avoid the allergen for a life. In many cases, it is necessary to control the intake of even the smallest trace amounts of product.

The question arises about the possibility of curative treatment. Specific immunotherapy with food allergens is being widely studied around the world as a method that provides protection against the development of a severe and life-threatening episode if the allergen is accidentally consumed by a patient who generally follows a strict elimination diet.

Oral immunotherapy (OIT) is the administration of a causative food allergen to a patient with proven sensitization and allergy on a regular basis in quantities. It is not cause a severe reaction, with a gradual increase in the dose of the product in order to achieve tolerance. OIT has been widely studied around the world, and it is clear that although it may generally have the desired effect, but the risk of developing an anaphylaxis reaction to OIT itself must be kept in mind [8].

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OIT is the most promising technique in the treatment of severe FA, but difficulties in its use are associated with many reasons:

- the risk of development of acute allergic reactions at the initial stage of treatment;
- differences in protocols (dose and rate of its increase);
- a lack of commercially available OIT drugs;
- a difficulty in diagnosing the onset of tolerance (as well as for allergen-specific immunotherapy with inhaled allergens, reliable and safe markers for testing the onset of effect have not been developed) [8].

There is an opinion that after achieving clinical success, OIT should be continued for a life, because a loss of effect is likely after ending of the therapy [8]. The possibilities of improving OIT by combining it with the administration of biological therapy (monoclonal antibodies: omalizumab, dupilumab) and with probiotics are also being studied. A final opinion on this issue has not yet been formed [8].

High-risk factors of undesirable consequences of OIT include:

- high degree of sensitization to the allergen, anaphylaxis in anamnesis (i.e., actually a direct indication for OIT);
- uncontrolled course of allergic disease;
- low compliance to the treatment regimen;
- presence of gastrointestinal forms of FA (eosinophilic esophagitis, food protein-induced enterocolitis syndrome) [8].

Due to these reasons, OIT is currently not authorized for use in the Russian Federation [1].

During childhood, patients with food anaphylaxis inevitably raise the question of the possibility of "disease outgrowth" and, consequently, of discontinuation of the diet, which is no longer required.

There are no reliable and highly safe methods either for diagnosing tolerance formation or for predicting the course of the disease as the child grows up.

ARE THERE RELIABLE METHODS FOR DIAGNOSIS OF FOOD ALLERGY?

The first and often most reliable way to diagnose FA is a structured anamnesis [9].

To complete the anamnesis data, methods for confirming sensitization are used, i.e. detection of specific IgE, free in serum or attached to effector immunocompetent cells, both *in vivo* and *in vitro*:

- AST;
- sIgE;
- basophil activation test (BAT), etc.

You must always remember that:

- these diagnostic methods confirm sensitization, and not the allergic disease itself.
- the cut-off level above which the test result in most cases is actually associated with the presence of an allergy to the product is only being studied for some of the most significant food allergens, such as CMP, egg [10];
- for different food products, the information content of the methods will be different; not all types of tests are available in a doctor's practice [9];
- none of the examination methods available in practice are without drawbacks; in addition, for a full interpretation of the results, studies performed on a local population are highly desirable [11].

The informativeness of methods for confirming sensitization depends naturally on the mechanism of FA in patient.

In the development of type 1 hypersensitivity reactions (atopic, IgE-mediated mechanism) to a food allergen, a typical pattern of clinical manifestations of the reaction is observed. The above-mentioned diagnostic tests for detection of IgE-sensitization in these situations are often highly informative and provide results that are easy to interpret and explain the patient's anamnesis [9].

Clinical characteristics of IgE-mediated food allergy include rapid onset of symptoms (from minutes to 2 hours after ingestion of the food allergen) reproducibility of reactions in dynamics with repeated contact with the same product and typical symptoms:

- urticaria, angioedema, itching of the skin, ears, palms, feeling of heat, hyperemia in pre-existing foci of dermatitis;
- itching, swelling of mucous membranes of an oral cavity, pharynx, nausea, vomiting, spasmodic abdominal pain, diarrhea;
- itching, swelling of conjunctivae, lacrimation;
- rhinorrhea, sneezing, nasal congestion, nasal itching, hoarseness of voice, stridor, cough, difficulty breathing, wheezing, cyanosis;
- pallor, cold sweat, palpitations, loss of consciousness and shock, tachycardia, arterial hypotension;
- anxiety, behavioral disturbances, irritability, apathy, lethargy, seizures, tremors, metrorrhagia;
- polysystemic reactions, including many of the above symptoms, up to lethal outcome (anaphylaxis).

The symptoms of IgE-mediated immediate-type FA are varied and Its interpretation depends on the clinical case. For example, the development of isolated seizures against the background of complete health is unlikely to make one suspect FA in the first place. Sneezing fits after consumption of a certain product are quite characteristic, although are not very common [9].

Clinical manifestations that develop by non-IgE-mediated and mixed mechanisms are more difficult to interpret. Based on the patient's complaints and anamnesis, a physician can identify a potential food allergen as the cause of symptom. But the informativeness of methods for detecting IgE-sensitization will be highly questionable.

Symptoms of non-IgE-mediated or mixed mechanisms of FA include [9]:

- contact dermatitis;
- gastrointestinal forms of FA (food protein-induced enterocolitis, allergic proctocolitis, allergic enteropathy);
- exacerbation of atopic dermatitis;
- eosinophilic esophagitis, gastritis, enteritis;
- exacerbation of bronchial asthma.

In clinical practice, it is not uncommon for patients with atopic dermatitis, suspecting food allergy, to have various tests to detect IgE-sensitization to food allergens by themselves, and upon receipt of the results exclude a number of foods from the child's diet. Based on this knowledge, the failure of this approach becomes clear. Particularly alarming are the situations when strict elimination diets are prescribed and number of important foods are excluded from the child's diet based only on laboratory tests, without sufficient analysis of clinical picture [9].

Patient education should emphasize that many variants of atopic dermatitis are not associated with FA. The search for causative food allergens is justified in patients with early-onset atopic dermatitis, in patients with severe atopic dermatitis at any age, and in patients with direct anamnesis data indicating a provocative role of food in the development of exacerbations [12]. However, it should be remembered that the absence of specific IgE does not exclude the diagnosis of FA [1].

In foreign practice, provocative test for food allergy diagnosis (PT) is often used after the sensitization confirmation step, which demonstrate the reaction to the suspected product under controlled conditions. PT is undoubtedly the "gold standard" in the diagnosis of FA. A particularly useful function of PT is to demonstrate tolerance to a product that has been excluded for a long time from the child's diet and feared to be introduced [9]. For practical purposes, an open PT is sufficient. In complex expert cases and in scientific studies, double-blind placebo-controlled PT is also used [9].

Due to technical complexity, lack of approved protocols for PT, and lack of standardized food preparations for PT, these tests are not performed in the Russian Federation [1].

In Russian practice, the so-called diagnostic introduction of a product is recommended as a diagnostic technique, i.e. trial introduction of small amounts of product previously excluded from the diet to assess clinical symptoms. Diagnostic administration is not used in children with anaphylaxis, when even minimal (trace) amounts of an allergenic product cause complaints. For diagnostic administration, a small amount of the product containing the suspected causative allergen is used, based on the anamnesis (the amount of the product for which the development of complaints was noted, the severity of the reaction to this amount). Start should be with a dose significantly lower than the one that led to the clinical manifestations of the allergic disease. The period of observation of the patient after diagnostic administration of the product depends also on the nature of previous reactions to this product and ranges from 2 hours in case of hypersensitivity of immediate type (urticaria, rhinitis, asthma) and to 2 days in case of hypersensitivity of delayed type (atopic dermatitis, gastrointestinal manifestations) in the anamnesis. If diagnostic introduction of the product did not lead to the development of symptoms, the product is introduced into the diet in gradually increasing amounts [1].

DOES A CHILD WITH BRONCHIAL ASTHMA NEED AN ELIMINATION DIET?

The prescription of diets with the elimination of a number of "highly allergenic" foods to children with bronchial asthma, allergic rhinitis and other respiratory allergic pathologies seems to be an important problem.

Bronchial asthma in childhood most often has an atopic mechanism. In some cases, the child's parents believe that food allergens provoke the symptoms of the disease. Thus, 180 children (of total 362 children aged from 6 to 18 years with atopic bronchial asthma) noted a provocative role of food in anamnesis. Among them, 70 children

were found to have positive sIgE to food allergens, and only 20 children had a positive PT [13].

Food allergens are seriously inferior to inhalant allergens (house dust, pollen, fur) [14, 15]. Even though the frequency of sensitization to this group varies from 0.8 to 25%. A significant proportion of these patients do not have clinical manifestations of food allergy, despite the detection of specific IgE in blood serum [14].

We present our own data on the analysis of the dispensary group of patients observed in the City Allergy Clinic of St. Petersburg (SPbFBO "Children's City Clinic No. 44"). The data of case histories and results of repeated examinations of 263 children diagnosed with bronchial asthma (BA, J45.0) at least 1 year ago were studied. The distribution of patients by age groups, comorbid diseases and severity is presented in Table 1.

After analysis of the data from case histories, it was found that 91 (34.6%) patients had positive (>0.35 IU/ml) specific IgE in serum to a small list of products (in descending order of frequency): chicken egg protein, milk (more often casein), cod, wheat, soy, and oats. During the directed questionnaire survey of patients (older than 7 years) and/or their parents, it was found that when consuming certain foods, the development of respiratory symptoms was repeatedly recorded in 16 people (6.1% of the examined sample), of whom 3 (18.75%) had no specific IgE detected in serum (reactions to fish and milk). Meanwhile, only nasal itching, serial sneezing, and watery rhinorrhea developed in 5 patients (31.25%) of the subgroup. All of them had positive specific IgE in serum. The remaining 11 patients (68.75%) had distant wheezing, dyspnea, serial cough in addition to rhinitis symptoms. Table 2 shows the clinical characteristics of subgroups of patients: patients in whom food consumption causes only an exacerbation of allergic rhinitis (AR) and comorbid bronchial asthma (BA) is exacerbated by inhalant allergens ("food AR"), patients in whom food consumption causes a combined exacerbation of both AR and BA ("food BA"), and patients without clinically significant FA ("no food allergy").

For patients in whom food consumption does not lead to respiratory symptoms, anaphylactic reactions have been described to insect stings and penicillin antibiotics. Patients with reproducible respiratory manifestations of food allergy (exacerbation of AR and/or an attack of BA) are usually younger and have polysensitization. Food sensitization has a delineated clinical picture even in the absence of specific IgE. Multisystemic manifestations in the structure of food anaphylaxis are more characteristic for "food BA" than for "food AR" (45.5% vs. 20%, a correct statistical

Table 1. Clinical features and medical history in examined patients

Таблица 1. Клинико-анамнестическая характеристика обследованных пациентов

Характеристика / Sign		Бронхиальная астма (263 пациентов), n (%) / Bronchial asthma (263 patients), n (%)
Возрастной интервал / Age interval	До 3 лет Under 3 years	22 (8,3)
	3–6 лет 3–6 years	71 (27,0)
	7–11 лет 7–11 years	97 (36,9)
	12–17 лет 12–17 years	73 (27,8)
Степень тяжести основного заболевания / Severity of the disease	Легкая / Mild	154 (58,6)
	Средняя / Moderate	81 (30,8)
	Тяжелая / Severe	28 (10,6)
Коморбидные заболевания / Comorbid diseases	Аллергический ринит / Allergic rhinitis	247 (93,9)
	Атопический дерматит / Atopic dermatitis	69 (26,2)

Table 2. Clinical features in patients with respiratory food allergy

Таблица 2. Клинические характеристики пациентов с респираторными проявлениями пищевой аллергии

Показатель / Indicator	Пищевой аллергический ринит, n=5 Food-induced allergic rhinitis, n=5	Пищевая бронхиальная астма, n=11 Food-induced bronchial asthma, n=11	Нет пищевой аллергии, n=247 No food allergy, n=247
Возраст, лет, Me [Q25; Q75] / Age in years, Me [Q25; Q75]	5,2 [4,1; 9,3]	7,3 [5,2; 14,6]	8,9 [6,5; 15,1]
Доля пациентов с атопическим дерматитом, n (%) / Patients with atopic dermatitis, n (%)	1 (20)	5 (45,5)	63 (25,5)
Доля пациентов с анафилаксией, n (%) / Patients with anaphylaxis, n (%)	1 (20)	4 (36,4)	2 (0,8)
Средняя суточная доза иГКС*, мкг, M±σ / Mean daily dose of inhaled glucocorticosteroid, mcg, M±σ	178,4±94,7	396,8±72,4	217,5±146,3

* Доза ингаляционных глюкокортикостероидов рассчитана по будесониду, согласно таблице эквипотентных доз GINA 2023 [16].

* Daily dose of inhaled glucocorticosteroid was calculated as budesonide equivalent, according to GINA 2023 dosing table [16].

comparison is impossible due to the small number of observations). Such clinical picture makes it necessary to strictly exclude the "guilty" product from the patient's diet for many years. However, in some children with normalization of laboratory parameters, trial allergen administration is possible.

Patients with respiratory complaints but without signs of food anaphylaxis often show a decrease or even absence of reaction to products after several years of elimination measures. In the study group, we identified 8 adolescent patients (12–17 years of age) with no dietary restrictions, clinical reactions to food and specific IgE to food allergens, who had a history of transient respiratory complaints to egg, milk, or fish during preschool age.

SHOULD HYDROLYZED ADAPTED FORMULA BE USED IN ARTIFICIAL FEEDING TO PREVENT FOOD ALLERGIES?

There are no absolutely effective techniques in the prevention of food allergy in young children. The most discussed measures for the prevention of FA are the support of breastfeeding until the age of 4–6 months, need for dietary restrictions for the expectant mother and lactating woman, and administration of hydrolyzed and partially hydrolyzed formula to children at risk (with aggravated heredity) who are artificially or mixed-fed. There are pros and cons for each intake, and the most balanced is the agreed position of domestic pediatricians, presented in the national clinical recommendations:

- there is no convincing evidence for the preventive effect of a strict hypoallergenic diet for a mother during pregnancy; a varied and nutritious diet is recommended for the expectant mother;
- exclusion of causative allergens is recommended for a mother if *she* suffers from an allergic disease;
- a breastfeeding mother of a child, who is at risk group, should be given a varied and complete diet with *restriction*, but not exclusion, of the most common allergens, including products containing CMP [1].

In 2020, the European Academy of Allergology and Clinical Immunology conducted a review of the evidence for FA prevention in children, excluding those recommendations for which the evidence base was not considered strong [17].

The experts support breastfeeding. They acknowledge with a low level of evidence the undesirability of introducing milk-based formula, but only for the time period in the first week of life. In fact, they explain that in the first 1–3 days of life, until the colostrum synthetized, if necessary, the baby should not be supplemented with milk-based formula without a recommendation. So what should be supplemented and how to continue feeding a newborn in the absence of breastfeeding after the age of 7 days?

The recommendations also include, with a moderate level of evidence, the introduction of

potentially allergenic foods such as chicken eggs and peanuts in the 1st year of life [18]. A systematic review of the literature did not show any adverse events or signs of any harm to children from feeding partially hydrolyzed formulas. The use of partially hydrolyzed formulas is associated with normal growth rates in children [19]. Thus, the recommendation to prescribe formulas based on partially hydrolyzed milk protein for prophylactic purposes to high-risk children who require artificial feeding is currently not supported or prohibited by European guidelines. The volume of evidence-based research is considered insufficient to produce any type of conclusion: neither pros nor cons. The "partial hydrolyzed" formula provides the same indicators of child growth and development as the standard formula, and is characterized by a high level of safety.

The agreed opinion of domestic experts is presented in the methodological recommendations of the Union of Pediatricians of Russia. There is currently no convincing evidence that hydrolyzed formula prevents the development of FA. Nevertheless, some studies demonstrate a reduction in the risk of atopic diseases in some children. In children at risk for atopy who are artificially or mixed-fed before 6 months of age, it is possible to use formula with reduced allergenic properties, particularly those based on moderately hydrolyzed milk protein. The effectiveness of such an intervention in children older than 6 months of age (e.g., after lactation cessation) has not been studied [20].

IS LATE INTRODUCTION OF COMPLEMENTARY FOOD JUSTIFIED FOR PREVENTION OF FOOD ALLERGY?

The opinion about the protective role of exclusive breastfeeding for the prevention of FA and the advisability of introducing the first complementary foods no earlier than the age of 6 months is widespread in different countries of the world.

In the French ELFE cohort (6662 children), the feeding patterns of children aged from 3 to 10 months were studied and information was collected on allergic diseases that developed by the age of 5.5 years. In this large cohort of children at both high and low risk of allergic disease, there was evidence that *failure* to introduce at least two "highly allergenic" foods by 10 months of age resulted in an increased risk of allergic conjunctivitis and food allergy (the reverse of the relationship, when allergenic foods are not introduced, because the child already had a food allergy, was controlled for in this study as a separate type of statistical error) [21].

Many experts believe that the introduction of complementary foods within the "window of tolerance" (from 4 to 6 months of age) helps to reduce the risk of developing atopy in subsequent years of a child's life [22, 23]. The key rule for the careful introduction of complementary foods in children at high risk of developing atopy is to prescribe monocomponent products of no more than 1 product per week. In general, the timing of introducing complementary foods should be the same as in healthy children [1, 23, 24]. From a "window of tolerance" perspective, oral tolerance induction should begin as soon as the child is able to accept foods other than breast milk (or formula), but before food allergy manifests. To start eating solid food, it is necessary to develop an interest in food, hold the head, sit with support, and lose the reflex of "pushing out the spoon" with the tongue. These conditions usually develop between 4 and 6 months of age. However, by this age the child may already be sensitized to food allergens and manifest an allergic disease. Thus, for some children the "window of opportunity" may be very narrow [25]. It is also unknown whether oral tolerance to non-IgE-mediated forms of FA can develop [25].

Key international studies, the 2015 LEAP and 2016 EAT studies, showed a reduction in the risk of development of peanut food allergy with early (4 to 11 months of age) introduction of peanuts into complementary foods in children at high and normal risk for allergic diseases, respectively [26, 27]. A meta-analysis of early egg introduction included 5 studies (1915 study participants) and found that introducing eggs into complementary foods between 4 and 6 months of age is associated with a lower risk of development of allergy to egg [28].

Regarding the early introduction of other complementary foods, there are mixed results from studies. The most studied allergenic complementary foods, peanuts, are not very important for Russia either as a cause of allergies or as a component of complementary feeding in the first year of a child's life. There are no guidelines for the early introduction of allergenic foods into the diet of children. There are also no commercially available dosed food supplements containing allergenic foods. There are no drugs to induce oral tolerance.

The global community is in the process of development an evidence-based, practical strategy for feeding of infants in the first year of life aimed at preventing of FA. Moreover, one of the important components of this strategy may, over time, be the early introduction of highly allergenic products [29]. Interventions aimed at the formation of oral tolerance through early dosed systematic introduction of highly allergenic foods into the diet of a child in the first half of the year have not currently been introduced in Russian pediatric practice [1].

Exposing the body to a variety of food antigens at a certain age may stimulate the formation of immunological tolerance. However, the protective effect of timely introduction of complementary foods can also be realized through the so-called Diet diversity, which is defined as the number of types of foods or food groups in a person's diet over a certain period of time. Studies, conducted in infants at the age of introduction of complementary foods, show a greater diversity of microbiota with a greater variety of diet, which, in turn, can lead to a decrease in the risk of allergies [30].

CONCLUSION

In the field of prevention, diagnosis and treatment of food allergies in children at the present time, there are significant unresolved problems.

1. Low awareness of primary care physicians about the difference between the detection of specific IgE and clinically significant food allergies.

2. Lack of protocols and approved recommendations for conducting PT in outpatient clinics.

3. Insufficient data on clinical and laboratory markers of the formation of food tolerance in patients with different mechanisms of pathogenesis (IgE-dependent and independent forms) and different clinical manifestations (gastrointestinal, skin, respiratory, systemic) of food allergy.

4. Limited therapeutic arsenal for acute allergic reactions to food (in particular, the lack of adrenaline autoinjectors).

5. Limited use of staged dietary expansion in patients who have achieved clinical remission of food allergy as a result of an elimination diet.

Nevertheless, the problem of food allergy continues to concentrate the efforts of both the international community and domestic scientists to conduct research and subsequently develop recommendations for the implementation of the results obtained in real clinical practice.

ADDITIONAL INFORMATION

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

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ROLE OF ORTHODONTIC PATHOLOGY IN THE FORMATION OF DYSPHAGIA

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Abstract. Orthodontic care for the population can be considered much more broadly than just bite correction. Malocclusion in somфe cases are accompanied by severe conditions such as dysphagia. When assessing the orthodontic status, this group of subjects has a distal jaw ratio, maxillary macrognathia, and deocclusion in the frontal area. These disorders can be either isolated or combined. A decrease in the volume of the upper respiratory tract is determined, which is associated with the distal position of the lower jaw. There are difficulties in pronouncing sounds. When providing care to such patients, an integrated approach is needed with the definition of a phased orthodontic treatment plan with a gradual transition from simple orthodontic devices to more complex ones in their design. A special place in the treatment and rehabilitation of such patients is played by functional correction devices, which simultaneously normalize the work of the muscles of the maxillofacial region and correct the bite. Early diagnosis helps to reduce the severity of pathology in patients starting from childhood. Treatment plans are offered, taking into account concomitant disorders. The use of orthodontic devices for muscle correction at the first stages allows you to gradually switch to treatment using non-removable equipment.Such a multi-level approach in the appointment of orthodontic devices makes it easier for the patient to adapt to the equipment, gradually complicating the design of the devices. It is not always possible to get the desired result, but there is always success in reducing the severity of the pathology. By correcting disorders, orthodontists, together with other clinicians, qualitatively change the patient's lifestyle and general health.

Keywords: *malocclusion, distal deep bite, open bite, dysphagia, violation of the volume of the upper respiratory tract*

РОЛЬ ОРТОДОНТИЧЕСКОЙ ПАТОЛОГИИ В ФОРМИРОВАНИИ ДИСФАГИИ

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Резюме. Ортодонтическая помощь населению может рассматриваться гораздо шире, чем только исправление прикуса. Аномалии окклюзии в некоторых случаях сопровождаются такими тяжелыми состояниями,

как дисфагия. При оценке ортодонтического статуса у этой группы обследуемых присутствует дистальное соотношение челюстей, макрогнатия верхней челюсти, дезокклюзия во фронтальном участке. Эти нарушения могут носить как изолированный, так и сочетанный характер. Определяется уменьшение объема верхних дыхательных путей, что связано с дистальным положением нижней челюсти. Имеются трудности в произношении звуков. При оказании помощи таким пациентам необходим комплексный подход с определением поэтапного плана ортодонтического лечения при постепенном переходе от простых ортодонтических аппаратов к более сложным по своей конструкции. Особую роль в лечении и реабилитации таких пациентов играют функциональные аппараты-корректоры, которые одновременно нормализуют работу мышц челюстно-лицевой области и исправляют прикус. Ранняя диагностика позволяет снизить тяжесть патологии у пациентов, начиная с детского возраста. Предлагаются планы лечения с учетом сопутствующих нарушений. Применение на первых этапах ортодонтических аппаратов для коррекции работы мышц позволяет постепенно переходить на лечение с применением несъемной техники. Такой многоуровневый подход в назначении ортодонтических аппаратов позволяет пациенту легче адаптироваться к аппаратуре, постепенно усложняя конструкцию аппаратов. Не во всех случаях возможно получить желаемый результат, однако всегда есть успех на пути снижения тяжести патологии. Проводя коррекцию нарушений, врачи-ортодонты вместе с другими клиницистами качественно меняют образ жизни пациента и его общее состояние здоровья.

Ключевые слова*: аномалия прикуса, дистальный глубокий прикус, открытый прикус, дисфагия, нарушение объема верхних дыхательных путей*

ROLE OF ORTHODONTIC CARE IN DENTISTRY

Nowadays, the section of orthodontic care plays a special role in a modern dentistry. A few years ago, the study of this specialty took place at departments of orthopedics, surgical dentistry and pediatric dentistry, with separate sections on orthodontic care. After some time, particular departments of orthodontic care began to be formed. Due to the fact that there were new devices and protocols for treatment of anomalies of dentition, different structure for the organization of educational and treatment processes was required. The former connection with other sections of dentistry allowed orthodontic care to be enriched with the experience of joint management of patients. Undoubtedly, it had a positive impact on deeper understanding of the etiology of many diseases and on preparation of comprehensive treatment plans for patients of different ages with concomitant diseases. Nowadays, orthodontists are the ones who develop a general treatment plan for each patient, determine not only disorders of stomatognatic system (SS), but also establish cause-and-effect relationships between severe bite disorders and changes occurring in swallowing, breathing, and musculoskeletal system.

Oral cavity is the beginning of digestive system, so pathological changes occurring there affect the health of all the humans body. It is established that diseases of hard dental tissues, periodontal tissues and SS primarily affect the work of a gastrointestinal tract, and also have a connection with other life-supporting systems of the body.

In children, detected disorders of SS allow an orthodontist to assess the degree of dental status of an oral cavity as a whole, to determine the reduction in the volume of oral cavity, position of the tongue at rest and during movements, and to identify a violation of the swallowing mechanism (Figs. 1, 2). As a rule, such patients have pronounced facial features, reduced height of the lower third of face; a lower jaw occupies posterior position, which, in addition to swallowing disorders, gradually leads to persistent formation of a decrease in the volume of upper respiratory tract. If there is no assistance in correcting the bite and normalization of other functions in early childhood, these disorders acquire the status of independent diseases when child grows up, and correction of the bite does not lead to correct functions of other systems.

During examination of oral cavity, doctors determine the presence of carious and non-carious lesions in the hard dental tissues. In such cases, if there is a bite pathology, patients are unable to bite food, chew and swallow it. Diseases of periodontal tissues, which are often diagnosed in adult patients, are manifested by a decrease in the level and density of bone tissue, bleeding gums, mobility of teeth and presence of mucosal traction. It leads to a change in the quality of food in consistency and composition, to decrease in chewing efficiency and with significant destruction of the ligamentous apparatus of tooth — loss of teeth,

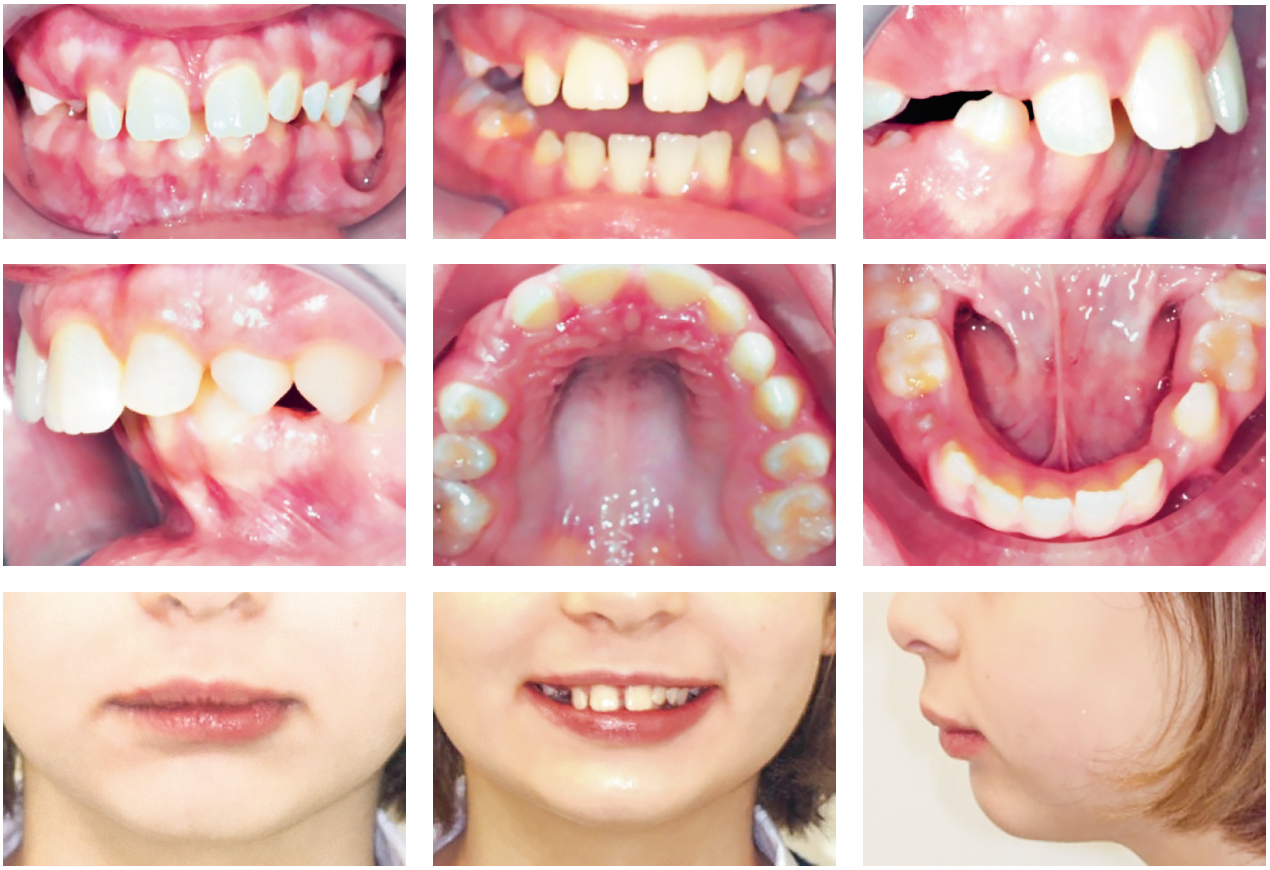

Fig. 1. The clinical situation in the oral cavity and the appearance of a patient with malocclusion. OB, OD with protrusion of incisors. There are irregularities in the position of individual teeth, narrowing of the jaws, and a change in their shape. There is no contact between the incisors, the swallowing pattern is disrupted due to a change in the position of the tongue and improper operation of the muscles of the maxillofacial region. The supramental fold is pronounced, the wings of the nose are not developed

Рис. 1. Клиническая ситуация в полости рта и внешний вид пациента с аномалией прикуса. Глубокий, травмирующий дистальный прикус с протрузией резцов. Имеются нарушения в положении отдельных зубов, сужение челюстей, изменение их формы. Отсутствует контакт между резцами, нарушен паттерн глотания за счет изменения позиции языка и неправильной работы мышц челюстно-лицевой области. Выражена супраментальная складка, крылья носа не развиты

which gives rise to secondary deformities of SS and face. The presence of skeletal anomalies of the bite with jaw deformity and malposition of teeth, violation of functions at early age, leads to more serious changes in the body of adult patients and failure in the work of many systems. Even if such bite anomalies are treated with orthodontic or combined methods, disorders that occurred during the period of exposure of this anomaly to the body are often isolated in an independent clinical form, and its treatment is not always successful after the correction of bite pathology.

Pathology of SS, namely bite disorders at the skeletal level, also affect breathing, swallowing and musculoskeletal system in general. If a person has some bite anomalies with disturbed relationship of the jaws, there is a shift in the center of gravity of the head, changes in the cervical spine. Posterior position of the lower jaw, narrowing of the upper jaw lead to a decrease in the volume of the oral cavity, violation of position of a tongue at rest and while moving. Such problem changes the swallowing pattern and leads to a decrease in the volume of upper airway [4]. That is why in orthodontic care, bite correction leads to significant improvement, normalization in the function of other organs and systems. Involvement of allied specialists in their profile issues is undoubtedly necessary to provide quality care to patients at any age.

NORMAL SWALLOWING AND MANIFESTATION OF DYSPHAGIA

Normally, swallowing is accompanied by closed lips and there is no tension of the muscles of the face and neck. Approximately the swallowing itself takes place within 0.2–0.6 s and performs about 600 times during the day [2]. In oral cavity, teeth

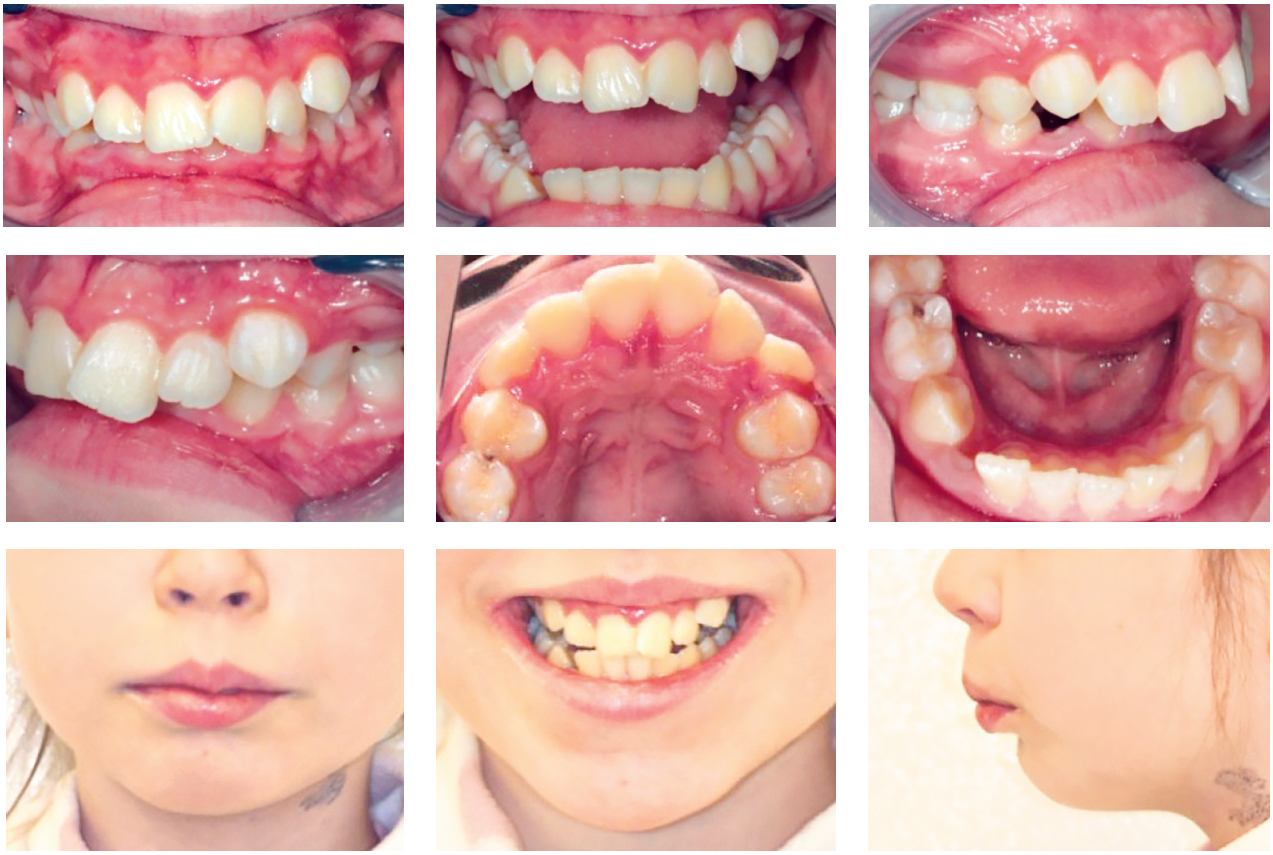

Fig. 2. The clinical situation in the oral cavity and the appearance of a patient with malocclusion. OB, OD with pronounced crowding of incisors. There is a pronounced crowding of teeth in the upper jaw, narrowing of the jaws, elongation of the anterior segment of the dental arch in the upper jaw and flattening on the lower. There is no contact between the incisors, the swallowing pattern is disrupted due to a change in the position of the tongue and improper operation of the muscles of the maxillofacial region. The supramental fold is pronounced, the lips close with tension, the wings of the nose are not developed

Рис. 2. Клиническая ситуация в полости рта и внешний вид пациента с аномалией прикуса. Глубокий, травмирующий дистальный прикус с резко выраженной скученностью резцов. Имеются резко выраженная скученность зубов на верхней челюсти, сужение челюстей, удлинение переднего отрезка зубной дуги на верхней челюсти и уплощение на нижней. Отсутствует контакт между резцами, нарушен паттерн глотания за счет изменения позиции языка и неправильной работы мышц челюстно-лицевой области. Выражена супраментальная складка, губы смыкаются с напряжением, крылья носа не развиты

are closed, and a total time of swallowing can take about 30–40 minutes for the entire temporal diurnal period. It has been found that during swallowing, potential of bioelectrical activity of the masseters and anterior fascicle of temporal muscles increases [1]. When the swallowing pattern is violated, depending on the degree of violation, the work of facial muscles becomes visible externally, mimic muscles are involved, changes in the tone of neck and back muscles occur. It is possible to change the posture of the body and appearance of head tilt. At the same time, the teeth may not close, tongue begins to contact the lips and cheeks [3]. Since the process takes not physiological but pathological way, there is a violation of stereotypes of muscles function of the maxillofacial region.

The "thimble symptom" is well known in children and characterized by disorders of muscles tone of perioral region if a child has an incorrect distal bite with transversal narrowing of the jaws and decrease in interalveolar height during swallowing. The pathological process of swallowing is carried out through laying a tongue between front teeth, which are not closed. As the result, positive pressure in the oral cavity appears and muscles both of perioral region and floor of the mouth, which are not characteristic for participation in this process, are included in the performance. They create tension in facial expressions when swallowing. As a rule, this bite abnormality does not allow the patient to bite food well, chew it, limits the movements of the tongue and forces it to take a wrong position at rest and disrupts the swallowing. This gradually leads to disturbances in function of many organs and systems, sometimes directly unrelated to the oral cavity. Consequent-

ly, in the long term, bite problems, accompanied by pronounced deformity of the jaw bones, lead to the development of both oropharyngeal ("high") and esophageal ("low") swallowing disorders, known as dysphagia. Two key mechanisms are known in the pathogenesis of dysphagia: obstruction and dysregulation. Methods such as pharyngeal examination, esophagography, esophagogastroscopy, and determination of a hydrogen index are used in the diagnosis of dysphagia. However, scientific articles almost never describe the state of the SS and its muscles.

In patients with diagnosed dysphagia, which is a persistent disorder, the act of swallowing itself is impaired. This is a secondary pathological process that develops against the background of other diseases and persistent changes, which include bite disorders. According to various literary sources, the prevalence of dysphagia is about 13%. It is detected in all age groups and tends to increase with age.

DYSPHAGIA AS COMMON SYMPTOM OF OROFACIAL MYOFUNCTIONAL DISORDERS

Orofacial myofunctional disorders (OMDs) are manifested by impaired muscle function and function of the facial region of the oral cavity.

OMDs can directly or indirectly affect breastfeeding, skeletal growth and facial development, chewing, swallowing, speech, occlusion, temporomandibular joint movement, oral hygiene, orthodontic treatment stability, facial aesthetics, and more.

Most OMDs occur due to inadequate nasal breathing with oral type of breathing and can manifest as dysphagia. OMDs can affect the treatment outcome of orthodontists, dentists, hygienists, speech therapists, and other professionals who work in the maxillofacial region.

OMDs can also be an etiologic factor in crossbite and bad habits: in some severe cases, it can cause sleep apnea (Fig. 3).

A study on how oral dysfunction can develop into malocclusion, acquired craniofacial disorder, and contribute to generational dysfunction, leading to disease, was conducted. Basic orthodontic consultations are usually recommended from the age of seven. However, the dysmorphic changes that lead to malocclusion often manifest much earlier. Similarly, after orthodontic treatment, patients require permanent fixation of the result when the bite is unstable, and without such retention, the malocclusion may return. The study provides an overview of the symptoms of OMDs and describes the oral functional areas that influence occlusal and facial development: breastfeeding, airway obstruction, soft tissue constriction, mouth breathing, oral position at rest, specific oral habits (swallowing, chewing). Aspects of the combined effects of OMD on the dentoalveolar complex over time and maternal disease on the developing fetus were also considered. As a result of the study, malocclusion and acquired craniofacial dysmorphology result from chronic oral dysfunction and OMD. Understanding the etiology and pathogenesis of the pathology, including open bite and impaired hard palate formation, is critical to achieve long-term stability.

The neurobiological study of swallowing and the dysfunction defined as dysphagia has been studied for two centuries, beginning with electrical stimulation applied directly to the central nervous system and then followed by systematic studies using specific interventions: transcranial magnetic stimulation, magnetoencephalography and functional magnetic resonance imaging. The field has evolved from mapping central neural pathways and peripheral nerves to identifying

Fig. 3. Manifestations of orofacial myofunctional disorders in the form of malocclusion, bad habits, sleep disorders (Source: https://ya.ru/images/)

Рис. 3. Проявления орофациальных миофункциональных расстройств в виде нарушения прикуса, вредной привычки, нарушения сна (Источник: https://ya.ru/images/)

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the importance of specific regions of the lower brainstem in terms of interneurons that provide sequential control of multiple muscles in the most complex reflex evoked by the nervous system, the pharyngeal phase of swallowing. Nowadays, there is an emerging understanding of how higher cortical areas interact with this brainstem control, providing a broader perspective on the process of functioning of the intact nervous system to control the three phases of swallowing (i.e., oral, pharyngeal, and esophageal).

RELATIONSHIP BETWEEN DYSPHAGIA AND BITE ANOMALIES

In the clinical picture, we see a combination of severe skeletal forms of dentofacial anomalies with disturbances in the function of muscles of the maxillofacial region, swallowing and breathing. The prerequisites for such disorders appears in childhood. Disturbances in muscle function, formation of malocclusion, and improper swallowing occur due to the influence of various etiological factors. At the age of four years, the first contact of small patient with an orthodontist may take place, and then a doctor can determine amount of orthodontic care required in order to eliminate or prevent existing disorders (Fig. 4, 5). At this stage, orthodontic functional removable appliances are used — OT-correctors. It allows to simultaneously normalize the pressure of the muscles in perioral area and muscles of the oral cavity, moving the lower jaw forward, providing it with the necessary genetically determined growth potential, and normalizing the swallowing (Fig. 6). The process of using such devices is quite simple. Children use them throughout the day under adult supervision. It takes 4–6 months to normalize functions. If there are associated problems, such as strands of the mucous membrane, short frenulum, correction is planned at an older age.

When patients come with the same problems, but already in the period of dentition, it is very important to help because this is one of the fastest and strongest periods of growth of the SS. If we cannot cover the full range of abnormalities that need to be treated further, our functional treatment will not be as effective and short in time. As a rule, patients have an occlusal anomaly in sagittal vertical line and jaw narrowing (Fig. 7). In the presence of bad habits of dysphagia, upper incisors are in protrusion. The use of various types of OT-correctors [6] can achieve results not only in the position of teeth and jaws, but also normalize function (Fig. 8).

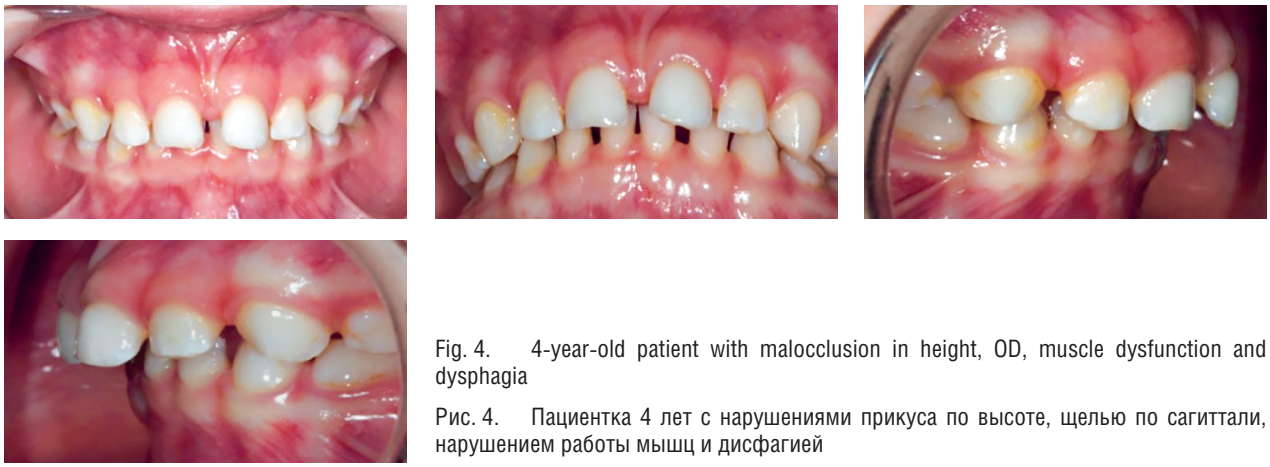

Fig. 4. 4-year-old patient with malocclusion in height, OD, muscle dysfunction and dysphagia

Рис. 4. Пациентка 4 лет с нарушениями прикуса по высоте, щелью по сагиттали, нарушением работы мышц и дисфагией

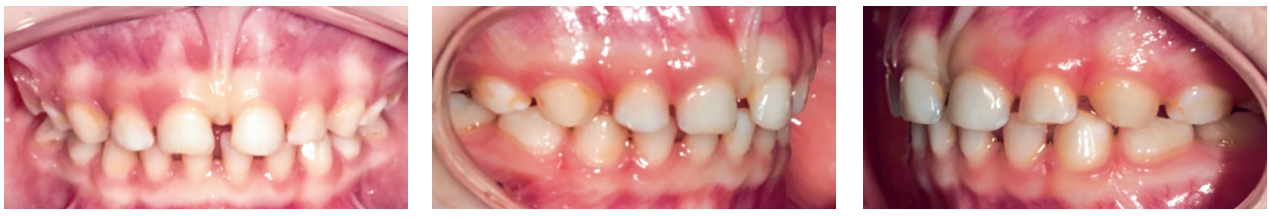

Fig. 5. A patient after orthodontic treatment. All violations have been eliminated

Рис. 5. Пациентка после ортодонтического лечения. Все нарушения устранены

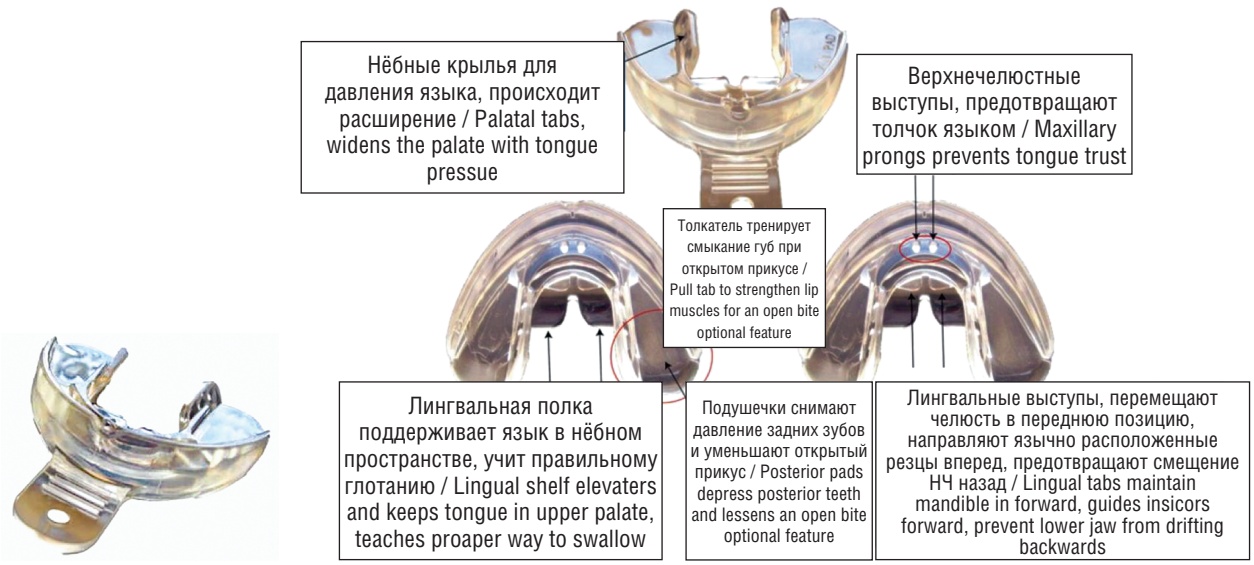

Fig. 6. The appearance — OT-corrector (in this case for patients with malocclusion and improper swallowing) with a description of its design features

Рис. 6. Внешний вид аппарата — ОТ-корректора вредных привычек (в данном случае для пациентов с аномалий прикуса и неправильным глотанием) с описанием его конструктивных особенностей

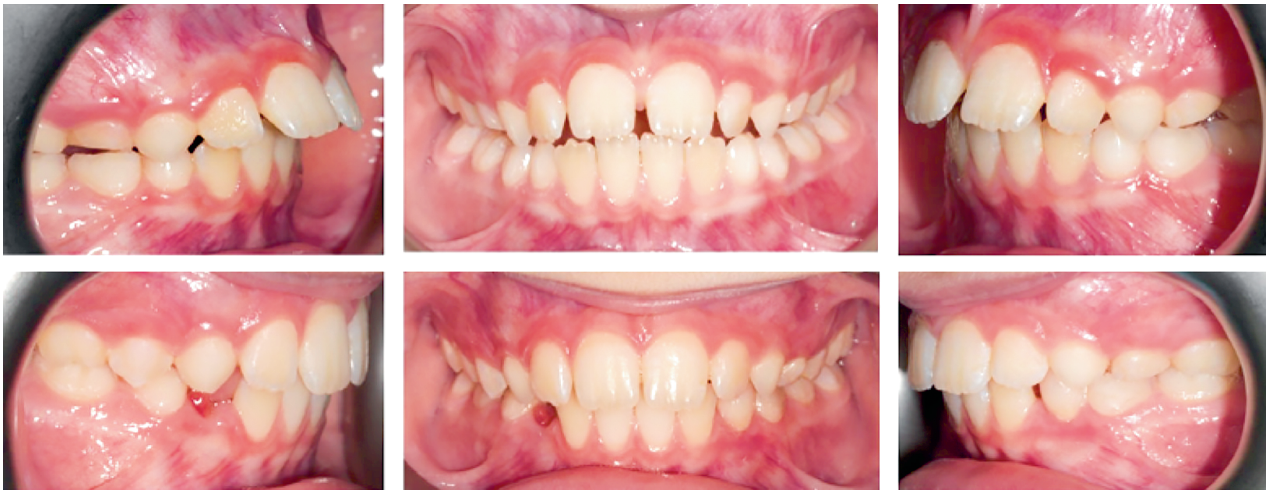

Fig. 7. Malocclusion complicated by dysphagia. The result of using OT-correctors throughout the year

Рис. 7. Нарушение прикуса, осложненное дисфагией. Результат применения ОТ-корректоров в течение года

Of course, the treatment protocol for such patients is complex and depends on the clinical situation and severity of the disorders.

In literary sources, there was a study that included children, adolescents and adult patients with a clinical diagnosis of "atypical swallowing" [5]. An association has been established between distal malocclusion, macrognathia, open bite and swallowing disorders. At the same time, some patients also had a posterior crossbite, and it was caused by a narrowing of the upper jaw along the transversal. Authors of the study concluded that "atypical swallowing" was associated with malocclusion.

Another study also focused on the causal relationship between an open bite in the frontal region and atypical swallowing [8]. These two frequently associated conditions are currently not fully understood and often accompanied by speech impairment, and present a problem for both young and adult untreated patients. It is noted that therapy for these complex cases may be orthodontic, speech therapy, or a combination. Different treatments were compared to determine effectiveness in improving skeletal health, normalization of muscle activity, and stability over time. Only clinical situations in the studied patients at the stage of dentition, i.e.,

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а/a *б/b* *в/c*

Fig. 8. Various types of OT-correctors: corrector of bad habits (*a*), Nite-Guide corrector (*b*), Occlus-O-Guide corrector (*c*), which are used to normalize bite and treat dysphagia during the period of replacement bite

Рис. 8. Различные виды ОТ-корректоров: корректор вредных привычек (*а*), Nite-Guide корректор (*б*), Occlus-O-Guide корректор (*в*), которые применяются для нормализации прикуса и лечения дисфагии в период сменного прикуса

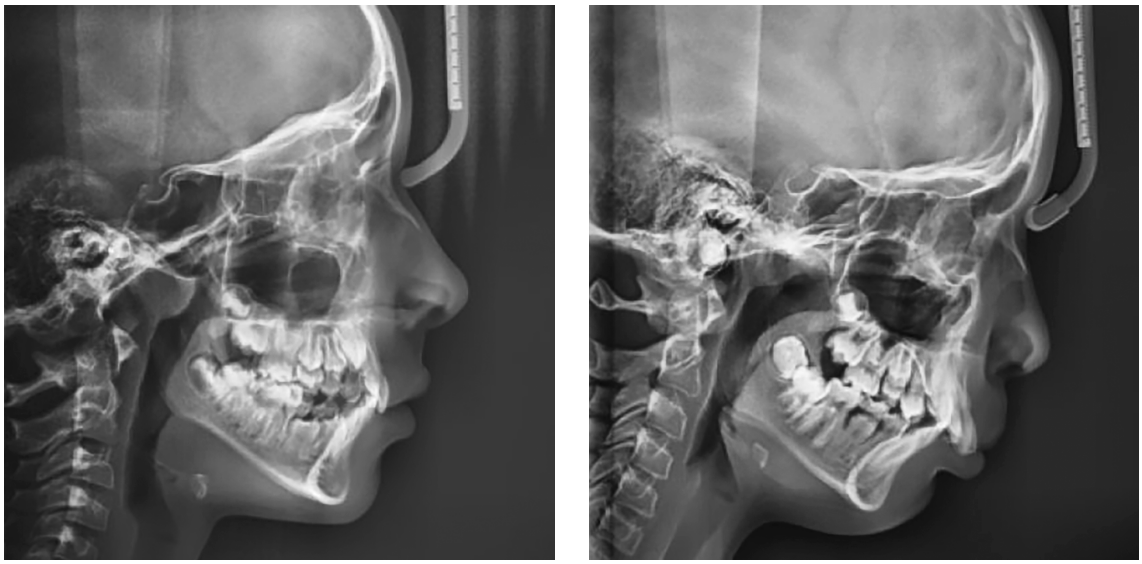
with deciduous or mixed dentition, with an anterior open bite related to the type of swallowing with the tongue positioned between the dental arches, were included. Patients underwent three different types of treatment: orthodontic only; myofunctional/logopedic only; combined). A combination of traditional orthodontic and myofunctional therapy was found to be the most effective treatment for anterior open bite associated with atypical swallowing. It was recognized that further research in this area is needed.

Thus, it is clear that there is a relationship between malocclusion, including open gnathic bite, which is always accompanied by a narrowing of the jaws, especially the upper jaw, and the position of the tongue, which affects swallowing. One of the ways to influence the correction of open bite in such cases is the expansion of the upper jaw. The study performed in 2023 evaluated swallowing in relation to oropharyngeal dysphagia (OD) in adolescents with maxillary transversal insufficiency and posterior crossbite with high palatal vault before and after rapid maxillary expansion (RME) [9]. Twenty patients (mean age 13.0±3.1 years) with bilateral posterior crossbite and high vaulted palate (RME group: RMEG) and 20 controls (mean age 13.4±2.6 years) with class I teeth crowding without posterior crossbite or high vaulted palate (control group: CG) were examined. Signs and symptoms of overdose were assessed using the Eating Assessment Tool-10 (EAT-10) questionnaire, patient complaints, and physical examination of swallowing before (T1) and 7 months after (T2) RME. Additionally, fiberoptic endoscopic evaluation of swallowing (FES) was performed. The prevalence of signs and symptoms of overdose based on patient complaints and physical examination of swallowing were low (5–15%). The investigators found no improvement in swallowing in patients with RME, which is apparently due to insufficient time for complete remodeling of the swallowing pattern.

The studies show a relationship of dysphagia and one of the most complex bite disorders, open in the frontal region, with a combination of crossbite in the lateral. Doctors have used methods to correct this skeletal disorder, but it had not fully cured dysphagia.

In the period of permanent bite, only functional therapy cannot help in achieving the desired goals, because the long-term deformation, which occurs under the influence of various etiological factors, leads to a persistent bite disorder in all planes. And disturbed swallowing, articulation functions only consolidate this pathology and make its treatment quite difficult. The lack of space for erupting teeth, which causes crowding, should be added. And the narrowing of the jaws fixes the distal position of the lower jaw, which aggravates the problem and affects facial features. A narrowing of the upper airway volume may occur (Fig. 9).

We observed a group of 12 patients (10–12 years old) with the diagnosis of "deep traumatic bite, distal bite, sharp narrowing of the tooth rows, severe crowding of incisors". Accompanying disorders were: dysphagia, respiratory disorders. In accordance with the treatment plan, they were fabricated appliances due to RME technique. This made it possible to expand the upper dentition in a relatively short period of time, eliminate crowding of teeth, allow the lower jaw to move forward, thus normalizing the volume of the oral cavity and swallowing.



a/a *б/b*

Fig. 9. Normal (*a*) and narrowed (*b*) airways

Рис. 9. Нормальные (*а*) и суженные (*б*) дыхательные пути

MULTIDISCIPLINARY APPROACH IN TREATMENT OF DYSPHAGIA IN ORTHODONTIC CARE

Atypical swallowing is a myofunctional problem consisting of a change in the position of the tongue during swallowing. Its high prevalence in population, multifactorial etiology and recurrent association with the presence of malocclusion have made it a subject of great interest and discussion in science. Scientists not only studied the possible association between atypical swallowing and malocclusion, but also looked for a solution to the problem: what type of therapy should be used in such cases? [7]. The review was conducted on the Medline database. Documents from 1990 onwards were examined, except cases with syndromes of central nervous system. A causal relationship between two problems was established, so, it was found that the habit of mouth breathing occurs as a mechanism to compensate for pre-existing malocclusion (especially in cases of open bite) and tends to aggravate cases of malocclusion. It has also been shown that tongue parafunction can adversely affect the course of orthodontic treatment.Thus, the best therapeutic approach seems to be a multidisciplinary one: in addition to orthodontics, which is necessary to correct the malocclusion, it is important to perform a myofunctional rehabilitation procedure to correct the oral breathing habit, which provides long-term permanent results. There was evidence of a significant difference between the results obtained with patients in the deciduous and shift bite. There was also evidence of a significant difference between results obtained with early (deciduous or primary mixed bite) or later treatment. A causal relationship between atypical swallowing and malocclusion has been established. Early diagnosis and surgical intervention have a significant positive effect on the outcome of therapy.

Another study shows the effect of early orthodontic treatment and myofunctional treatment in children with erupting teeth on the correction of anterior open bite, as well as on the normalization of breathing, swallowing, and tongue position [10]. Interventions used to correct anterior open bite and other muscle functions such as breathing/swallowing and tongue position were compared. Quality assessment was based on the Cochran method for assessing the risk of displacement. Random-effects meta-analyses were performed to assess treatment effects. In 265 initial search results, 15 articles were included in the review. Eight were randomized controlled trials (RCTs) and 7 were controlled clinical trials. Treatment outcomes included skeletal and dentoalveolar changes recorded cephalometrically, normalization of mouth position and lip closure, improvement in tongue positioning at rest/pressure and modification of swallowing patterns. There was no evidence to support the use of lingual stop

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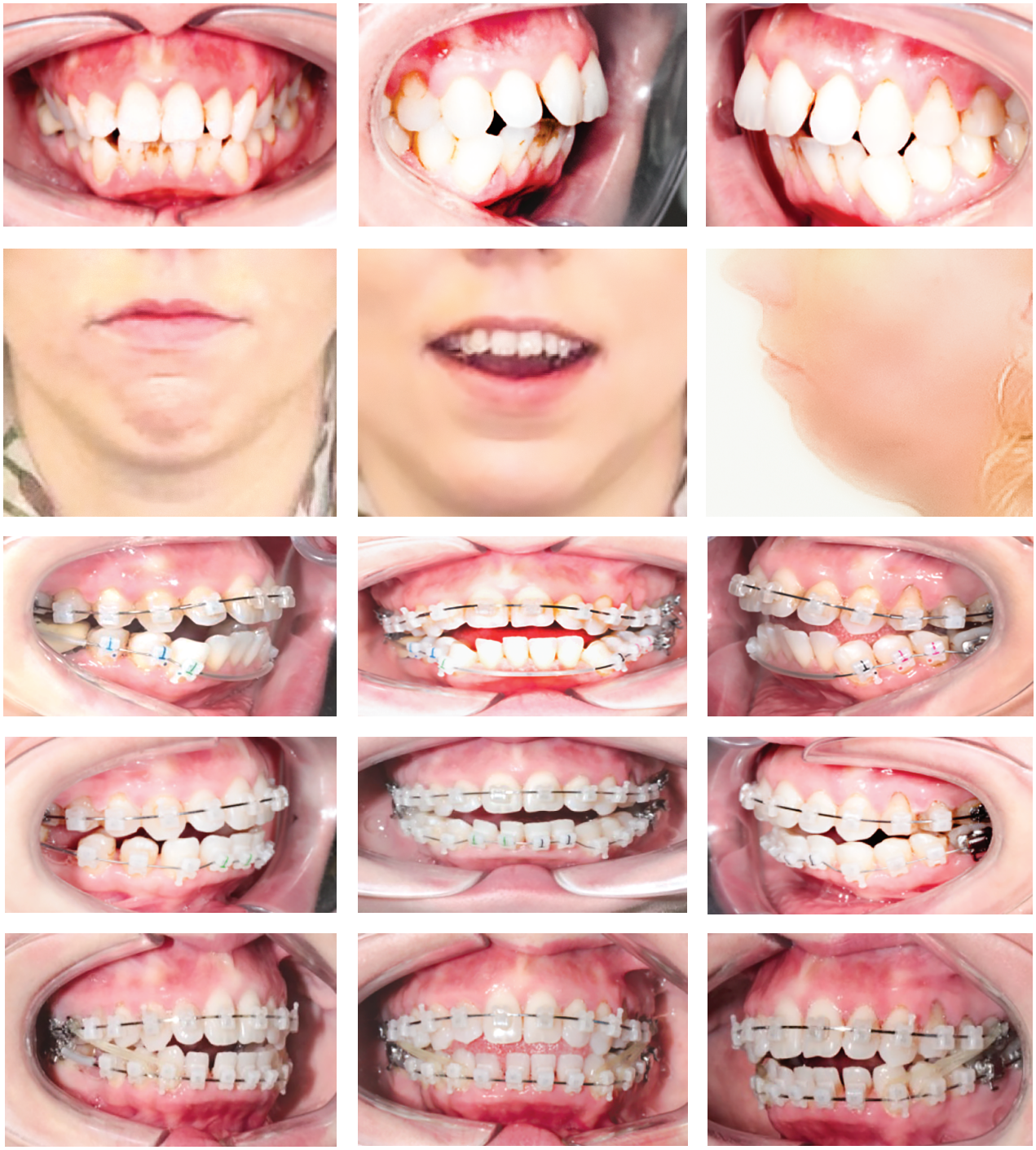

Fig. 10. Stages of treatment of a patient with orofacial myofunctional disorders, malocclusion, dysphagia

Рис. 10. Этапы лечения пациента с орофациальными миофункциональными расстройствами, аномалией прикуса, дисфагией

appliances instead of fixed appliances for correction of anterior open bite in children with a shift bite (SMD –0.03; 95% CI 0.81–0.74; p=0.94). It was concluded that early orthodontic and myofunctional treatment in children in the dentition and shift dentition appears to be a promising approach, but no proven single treatment method has been established.

According to our clinical data, if a patient with OMD bite anomalies, including dysphagia, needs treatment from an orthodontist as an adult, we see a complex pathology that, in addition to traditional orthodontic treatment, requires myofunctional therapy. According to our clinical observations, the most complex group of patients is the one with a combination of vertical discrepancy,

Fig. 11. The relationship of the occlusion anomaly with disorders of other important body processes

Рис. 11. Взаимосвязь аномалии окклюзии с нарушениями других важнейших процессов организма

namely open bite with vertical growth type and dysphagia (Fig. 10). The orthodontic treatment plan involves a compromise variant with improvement of bite parameters and changes in muscle tone. This combination of fixed appliances and myofunctional therapy helps to reduce the severity of pathology with unchanged facial features.

Thus, a multidisciplinary approach, combined orthodontic and myofunctional treatment, is suggested in patients with OMD, severe dysphagia, and bite anomalies (Fig. 11). Only in this case the position and function of the tongue is improved, effect on the bite towards its normalization and thus eliminating some of the causes contributing to dysphagia. However, no clear answer with treatment protocols has yet been developed, although all studies confirm that treatment should be started as early as possible.

CONCLUSION

Manifestation of dysphagia is always present in bite anomalies such as deep distal bite and most pronounced in open bite in the frontal region. These are skeletal abnormalities with lateral narrowing of the maxilla and posterior positioning of the mandible. In this case, there is a violation of the position of tongue at rest and in movement, violation of articulation and the work of the muscles of maxillofacial region, narrowing of the upper airways. In general therapy it is necessary to expand the upper jaw, thereby increasing the volume of the oral cavity and changing the position of the tongue. At the same time, it is recognized that better works integrated approach, aimed not only at correcting the bite, but also to normalize the work of muscles of the dento-mandibular-facial region. These therapeutic measures are more successful at an early age with the use of elastomeric correctors. They allow to simultaneously work on the correction of the bite and normalization of the tongue position, which leads to elimination of dysphagia. In the period of replacement bite, RME appliances have proved to be a good solution at the first stage of treatment. Thereafter, the use of fixed appliances and elastomers is also justified. Adult patients have the least potential to benefit from correctors, as they have persistent pathological disorders. The use of fixed appliances can partially solve the issues of bite correction. There is a need for further clinical research on this topic in all age groups.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

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DIETARY CORRECTION OF OBESITY IN CHILDREN AND ADOLESCENTS

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Abstract. Optimization of nutrition is one of the main components of obesity therapy in patients of all age groups. In children and adolescents, dietary correction of obesity is especially important due to the limitations of medical and surgical treatments. The goal of diet therapy for obesity in children is not only to reduce body weight, but also to provide the body with the nutrients necessary for further growth and development. Currently, the long-term use of hypocaloric diets is not recommended in outpatient practice for obese children due to their negative effect on nutritional status and quality of life. The method of choice is an individual isocaloric ration with sufficient protein content and control of carbohydrates and/or fats, compiled taking into account food tolerance and taste preferences of the child. It is necessary to educate patients to form a stereotype of healthy eating and adequate eating behavior in later age periods. A promising therapeutic strategy can be considered the supplementation of nutrients that are key to nutritional status. The article presents modern approaches to dietary therapy of obesity in children and adolescents, which make it possible to ensure long-term adherence to treatment for patients and their families.

Keywords: *obesity, children, nutrition, diet therapy*

ДИЕТИЧЕСКАЯ КОРРЕКЦИЯ ОЖИРЕНИЯ У ДЕТЕЙ И ПОДРОСТКОВ

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Резюме. Оптимизация питания является одним из ведущих компонентов терапии ожирения у пациентов всех возрастных групп. У детей и подростков диетическая коррекция ожирения имеет особое значение в связи с ограничениями медикаментозных и хирургических методов лечения. Целью диетотерапии ожирения у детей является не только снижение массы тела, но и обеспечение организма нутриентами, необходимыми для дальнейшего роста и развития. В настоящее время в амбулаторной практике для детей с ожирением не рекомендуется длительное использование гипокалорийных диет в связи с их негативным действием на пищевой статус и качество жизни. Методом выбора является индивидуальный нормокалорийный рацион с достаточным содержанием белка и контролем содержания углеводов и/или жиров, составленный с учетом переносимости пищевых продуктов и вкусовых предпочтений ребенка. Необходимо обучение пациентов для формирования стереотипа здорового питания и адекватного пищевого поведе-

ния в дальнейшие возрастные периоды. Перспективной терапевтической стратегией можно считать дотацию ключевых для пищевого статуса нутриентов. В статье представлены современные подходы к диетотерапии ожирения у детей и подростков, позволяющие обеспечить длительное сохранение приверженности к лечению пациентов и их семей.

Ключевые слова: *ожирение, дети, питание, диетотерапия*

INTRODUCTION

The main component of treatment strategy for obesity in children and adolescents is non-drug therapy aimed at lifestyle modification, including nutritional correction, increased physical activity and normalization of eating behavior [1]. Non-medication treatment has proven efficacy and safety, but requires strong motivation of each patient and his/her family for long-term, in many cases for many years, adherence to the recommendations in present obesogenic (obesity-promoting) environment. The goal of nutritional therapy for obesity is to reduce the excess energy value of food, which allows, in combination with adequate physical activity, to achieve a negative energy balance.

Since the beginning of the XXI century, the approach to the nutrition of obese children and adolescents has changed dramatically. In Russian and international medical practice, strict food restrictions have been replaced by healthy eating rules designed to form of new dietary habits in patients and their families [2, 3]. The Russian clinical guidelines for the treatment of obesity in children enshrine the leading role in the dietary therapy of obesity of a normocaloric diet that meets the age-sex requirements of each child in energy and nutrients [2]. Nowadays, all types of diets (hypocaloric, ketogenic, with a reduced glycemic index, etc.) are considered to be alternative options of diet therapy, which are used according to the indications, limited in time courses and often in hospital.

HYPOCALORIC DIET

The traditional approach in the treatment of obesity in children for many decades was the prescription of a hypocaloric diet with a reduction in energy value at the expense of fats and carbohydrates. This method was based on the classical diet no. 8 according to the system of M.I. Pevsner and was recommended for both inpatient and outpatient use [4]. Most researchers noted the low effectiveness of the hypocaloric diet in the long term for patients, who used it at home [5], but this fact was often because of lack of discipline and willpower. However, long-term implementation of strict recommendations, including prohibition of a wide range of foods and dishes, calorie counting, regulated diet without taking into account individual food preferences, in the absence of professional psychological support was accompanied by a significant reduction in the quality of life as a result of hunger and impaired social functioning associated with food restrictions.

The hypocaloric diet is currently considered to be the diet of choice for the treatment of obesity in hospital [3]. It can be used in courses to reduce body weight rapidly in case of morbid obesity and/or if a patient has severe complications that are not amenable to drug therapy (for example, obstructive sleep apnea syndrome). Rapid weight loss is also necessary in preparation for surgical treatment requiring general anesthesia.

This diet is characterized by a reduced content of simple carbohydrates and saturated fat. The amount of protein in the diet should correspond to the age norm or be slightly increased, and the reduction of energy value is achieved by reducing the content of carbohydrates and partially fats [1]. The example of hypocaloric menu for children in hospital is presented in Table 1.

The maximum weight loss using this method of diet therapy is noted in the first 3–5 days of inpatient treatment. It is associated with an increase in diuresis: during the transition from home food, which in most families is characterized by a high content of table salt, to a diet with normal sodium content.

In obese children, controlling protein intake requires special attention. Protein meals provide a sense of satiety, making dietary regimens easier to tolerate. Ensuring adequate protein intake in hospital settings can be difficult. Unfamiliar flavors of food, limited assortment of dishes, including meat and fish, often lead to children's refusal to eat, which causes a deficit in the intake of essential nutrients. Within the framework of a standard hypocaloric diet with regulated cooking technology, fish and egg dishes, vegetable side

Table 1. Sample menu of a hypocaloric diet for school-age children

Таблица 1. Примерное меню гипокалорийной диеты для детей школьного возраста

Наименование блюда / The course	Выход в г/мл / Quantity in gr/ml
I Завтрак / I Breakfast	
1. Омлет натуральный, фаршированный зеленым горошком / Natural omelette with green peas.	130
2. Салат из помидоров и огурцов с растительным маслом / Tomato and cucumber salad with vegetable oil.	115/5
3. Компот из сухофруктов / Dried fruit compote.	200
II Завтрак / II Breakfast	
1. Суфле из моркови с творогом / Carrot soufflé with cottage cheese.	215
2. Чай / Tea.	200
Обед / Dinner	
1. Суп рисовый с овощами вегетарианский, ½ порции / Vegetarian rice soup with vegetables, ½ portions.	250
2. Мясо отварное без соли / Boiled meat without salt.	55
3. Брокколи отварная с растительным маслом / Boiled broccoli with vegetable oil.	155/5
4. Сок фруктовый (абрикосовый) / Fruit juice (apricot).	200
Полдник / Afternoon snack	
1. Отвар шиповника / Rosehip decoction.	200
2. Яблоко печеное без сахара / Baked apple without sugar.	1 шт.
Ужин / Supper	
1. Рулет мясной запеченный / Baked meat roll.	105
2. Салат из свежей капусты и моркови с растительным маслом / Fresh cabbage and carrot salad with vegetable oil.	130/5
3. Чай / Tea.	200
На ночь / For the night	
1. Кефир 1% / Kefir 1%	200

Дополнительно: / Additionally:

Хлеб ржаной / Rye bread 100

Энергетическая ценность: 1628 ккал / *Energy value:* 1628 kcal

dishes and salads are the least popular. Children with selective appetite and with established stereotypes of irrational nutrition may completely skip meals consisting of subjectively unacceptable for them foods and dishes. Insufficient adherence to nutritional therapy in such patients leads to a decrease in protein and dietary fiber intake [6].

It should be remembered that the use of a strict hypocaloric diet, especially in the absence of sufficient physical activity in the hospital, may lead to a decrease in the fat-free components of body composition and be the cause of lower resting energy expenditure in the long term [7–9].

There is a high risk of reducing fat-free components of body if patient uses a hypocaloric diet combined with hypodynamia. It limits the indications for long-term treatment of obesity in hospital [8, 10, 11]. Previously, it was believed that treatment of obesity, regardless of its degree and the presence of complications, should be started in an inpatient clinic to "isolate" the child from the adverse effects of the family's dietary habits [12]. There was an opinion that in hospital a child is taught discipline and a proper dietary regimen. However, in practice, the low motivation to reduce body weight in children, especially preschoolers and younger schoolchildren, does not allow the formation of individual responsibility under conditions of strict food restrictions. It should be remembered that the use of a strict hypocaloric diet, especially in the absence of sufficient physical activity in hospital conditions, can lead to a decrease in fat-free components of the body and, in the long term, be the cause of a decrease in resting energy expenditure [7–9].

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The high risk of reducing fat-free components of body composition in children using a hypocaloric diet combined with hypodynamia limits the indications for long-term inpatient treatment of obesity [8, 10, 11]. Previously, it was believed that treatment of obesity, regardless of its degree and the presence of complications, should be started in an inpatient setting to "isolate" the child from the adverse effects of the family's dietary habits [12]. There was an opinion that inpatient hospitalization the child is taught discipline and a proper dietary regimen. However, in practice, the low motivation to reduce body weight in children, especially preschoolers and younger schoolchildren, does not allow to form individual responsibility in the conditions of strict food restrictions. In the past, so called fasting days were considered a mandatory component of treatment of obesity in both children and adults [4, 13]. In essence, it was a mono-diet used for one day. Both protein (kefir, cottage cheese, boiled meat) and carbohydrate (fruits, vegetables) models of nutrition were used to reduce energy intake. There was an opinion about the usefulness of "cucumber" and "watermelon" fasting days. Such one-day restrictions were recommended to be practiced at least once a week. At present, this approach to dietary therapy of obesity cannot be recognized as acceptable due to its nonphysiologic nature, lack of evidence, and negative impact on metabolism. Despite significant restriction of energy intake, nutrient imbalance leads to abnormalities in body composition. Therefore, the ostensible effectiveness of fasting days has often been attributed to dehyd-

Table 2. Sample menu of an isocaloric diet for school-age children

Таблица 2. Примерное меню нормокалорийной диеты для детей школьного возраста

Наименование блюда / The course	Выход в г/мл / Quantity in gr/ml
I Завтрак / I Breakfast	
1. Язык отварной / Boiled tongue.	75
2. Каша гречневая рассыпчатая с растительным маслом / Buckwheat porridge with vegetable oil.	170/10
3. Кофе с молоком / Coffee with milk.	130/50
II Завтрак / II Breakfast	
1. Творог свежеприготовленный / Freshly prepared cottage cheese.	100
2. Яблоко печеное с ягодами без сахара / Baked apple with berries without sugar.	1 шт.
Обед / Dinner	
1. Борщ вегетарианский со сметаной / Vegetarian borsch with sour cream.	500/10
2. Бефстроганов из отварного мяса / Boiled beef stroganoff.	55/60
3. Картофельное пюре с растительным маслом / Mashed potatoes with vegetable oil.	200/10
4. Маслины / Olives.	30
5. Компот из ягод с сахаром / Berry compote with sugar.	200
Полдник / Afternoon snack	
1. Отвар шиповника без сахара / Rosehip decoction.	200
2. Фрукты свежие / Fresh fruits.	200
Ужин / Supper	
1. Рулет мясной, фаршированный омлетом / Meat roll stuffed with scrambled eggs.	125/5
2. Винегрет овощной с растительным маслом / Vegetable vinaigrette with vegetable oil.	150/10
3. Биточки морковно-яблочные / Carrot and apple cutlets.	180
4. Чай / Tea	180
На ночь / For the night	
1. Йогурт / Yoghurt.	125
2. Курага размоченная / Soaked dried apricots	60

Дополнительно: / Additionally:

1. Хлеб ржаной / Rye bread	100
2. Хлеб пшеничный / Wheat Bread	120

Энергетическая ценность: 2630 ккал / *Energy value:* 2630 kcal

ration of the body [14]. Exclusion of protein from the diet is particularly dangerous because it promotes mobilization of protein from depots, which are primarily skeletal muscles. Current knowledge about the high frequency of sarcopenic obesity in all age categories and its role in the development of comorbid pathology proves the danger of protein exclusion from the diet even for a short period of time [7, 8, 15, 16]. In addition, excessive fructose consumption when using popular "apple" and "fruit" fasting days is an important etiologic factor in the development of nonalcoholic fatty liver disease [17].

NORMOCALORIC DIET

Prolonged treatment of obesity in pediatric patients is accompanied by certain difficulties, because it requires not only creating an energy deficit, but also providing the body with nutrients necessary for further growth and development. For example, in children, you cannot sharply limit the fat component of the diet due to the need for it to form an adequate hormonal background in puberty. And the restriction of meat products can increase the risk of anemia in adolescent girls. The safest and most effective method of dietary therapy of obesity in children at the outpatient stage is a normocaloric diet corresponding to the patient's age-specific needs for energy and nutrients [18].

It should be noted, that the diet used to correct obesity is not a short-term diet, at the end of which the patient can return to the usual style of eating. Due to the need for long-term compliance with the new nutritional rules in outpatient clinics, it requires individualization of recommendations, taking into account the food preferences of a particular patient while maintaining the norm of energy and nutrient intake. This approach allows maintaining normal growth and development rates, as well as maintaining high physical and intellectual activity [1]. An example of a normocaloric menu for children is shown in Table 2.

To ensure maximum individualization of nutritional therapy, it is recommended to make a diet on the base of nutritional status of each patient. The energy value of the diet should correspond to the actual energy expenditure of the child. "The gold standard" for determining individual values of basic energy metabolism and oxidation rate of macronutrients is indirect calorimetry [19]. Amount of nutrients is established depending on the individual metabologram values. The importance of determining metabolic requirements is determined by the high frequency of violations of their values in children. Thus, about half of obese children have an increased rate of fat oxidation associated with its excessive amount in the usual diet. This feature indicates that there is no need for a sharp restriction of fats, especially unsaturated fats, in the diet of an obese child.

Indirect calorimetry is not a commonly available method. Therefore, calculated formulas can be used to determine the daily energy value of the diet. In obese children, it is recommended to estimate the level of basal metabolism using the Shoefild formula, taking into account age and sex [18]. When calculating the daily energy value of the diet, it is necessary to focus on the level of physical activity of the patient. To determine the daily energy requirement of individuals with a low level of physical activity, the index of resting energy expenditure is multiplied by a coefficient of 1.4, with an average level — by 1.6, with a high level of physical activity — by 1.9.

In children with a low obesity class in the absence of complications, general age-sex norms of energy and nutrient intake can be used, as given in the guideline "Norms of physiologic needs in energy and nutrients for different population groups of the Russian Federation" (2021) [18].

The daily ration of a child should be distributed in such way, that the main part of it falls on the first half of the day, i.e. the hours of greatest motor activity. The last meal should be at least two hours before bedtime.

In formulating diets for obese children, a number of basic rules should be adhered to in order to achieve optimal nutrient intake without severe restriction or prohibition of any foods and meals that do not allow long-term adherence to the recommendations. A complete ban may be appropriate only for the group of sweet soft drinks with added sugar, which includes not only carbonated beverages, but also commercially prepared juices/nectars, bottled tea, morsels, and kvass [20, 21].

A child's daily menu should contain lean meat (beef, veal, rabbit, chicken, turkey), fish (cod, hake, pink salmon, etc.), eggs, and low-fat milk and dairy products, including in the form of fermented milk drinks. However, milk and dairy products with a high fat content (milk with a fat content of more than 3.2%, cream, sour cream with a fat content of 20% or more, cottage cheese with a fat content of more than 5%, cottage cheese desserts, glazed cottage cheese, cottage cheese mass, cheese varieties with a fat content of more than 40%)

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should be limited in the diet of obese children and used no more than 1–2 times a month.

In the diet should be sharply limited the use of any sausages, wieners, refractory animal fats (beef, mutton, pork), trans fats (margarine). The amount of butter can remain within the age-appropriate range.

Vegetable oil intake should be in line with age-related needs. A diet containing adequate amounts of vegetable fats helps to reduce hunger. Vegetable oil should be used in its natural form: for salad dressing, vinaigrettes. It can be added to dishes cooked without fat.

Modification of the carbohydrate component of the diet in obese children requires special attention. The quota of simple carbohydrates is reduced by significantly limiting foods with a high glycemic index in the diet: added sugar, confectionery, bread, primarily made of refined flour. According to current Russian norms, the daily intake of added sugar should not exceed 10% of the energy value of the diet, and for overweight and obese persons it is recommended to reduce the intake of added sugar to ≤5% of the daily energy intake. Thus, obese children should limit added sugar to 2–3 teaspoons per day.

Vegetables and fruits form an important part of the diet. Dietary fibers in fruits and vegetables stimulate intestinal peristalsis, contribute to the regulation of lipid metabolism, and are a substrate for normal gut microbiota. Foods rich in dietary fiber create a feeling of satiety. Fruits and vegetables provide the child's body with minerals and vitamins, have a diuretic effect, removing excess fluid from the body. In this regard, the diet should include cucumbers, cabbage (white, cauliflower, Brussels, kohlrabi), zucchini, tomatoes, pumpkin, radishes, carrots, turnips, asparagus, leafy salads, unsweetened fruits and berries. It is advisable to include in the diet several times a day dishes of raw and cooked vegetables (salads, vinaigrettes with vegetable oil, boiled and stewed vegetables, etc.). The amount of potatoes should be limited to 1/2–1/3 of the recommended rate, replacing it with other vegetables. Potatoes are cooked in baked or boiled form. Fried potatoes and mashed potatoes with butter are not included in the diet.

In the diet of obese children should not be used sours, canned compotes, fruit purees, including homemade. Preference should be given to natural fresh fruits and berries without added sugar. In the absence of fresh seasonal vegetables, berries and fruits should be used frozen products.

Food is cooked in boiled, steamed, grilled, baked ways. In the diet of obese children, we do not use dishes fried in oil, deep-fried. Surface frying on a dry pan or with a minimum of vegetable oil is allowed (it is recommended to use spray oil).

First meals should be predominantly vegetarian. Meat, chicken, mushroom and fish broths are limited in the diet of an obese child. Meat and fish dishes are given in the form of boiled portioned pieces or in the form of steamed cutlets, beaters, meatballs. As garnishes for second courses it is recommended to use a variety of vegetables or crumbly porridge: buckwheat, pearl, oatmeal and millet. Rice, potatoes, pasta from durum wheat varieties are included in the menu no more than once a week.

Eggs (for chicken eggs — no more than 1 per day, 3 per week) should be hard-boiled or used for cooking [22].

According to current national clinical guidelines, the necessary conditions for effective treatment include:

- restriction of sweet drinks: prohibition (consumption of no more than 1 portion and no more than once a week) not only of sparkling sweet drinks, but also of juices, compotes, morsels with permission to take drinking water at the child's request;
- limit in sweet fruits — up to 1 serving (100 g) per day;
- at least 4 meals a day, breakfast is compulsory;
- prohibition of sweet dairy products;
- control of portion size/number of servings; "food plates" are now widely used to show the desired portion size. If a child wants to eat a second portion of lunch/dinner allow it 20 minutes from the first, provided it is eaten regularly (at least 4 meals a day);
- enriching the diet with vegetables (300 g for young children and 400 g per day for adolescents, limiting the use of potatoes as the only vegetable in such quantities), dietary fiber, whole-grain products;
- teaching children to eat slowly without computer/TV/mobile phone [2].

Forcing a child to consume certain foods that are considered healthy but have ambiguous organoleptic characteristics depending on the method of cooking (fish, lean meat, cruciferous vegetables, etc.) can lead to negative attitudes toward these foods. If a food is strictly prohibited, it is more likely to be consumed in excess in the absence of control.

ALTERNATIVE DIET THERAPIES

These diets are used for short-term prescription to accelerate weight loss and increase patients' motivation. Currently authorized approaches in children include hypocaloric diets, ketogenic diets, and reduced glycemic load diets.

Ketogenic diet

The main objective of the ketogenic diet is to reduce the carbohydrate component of the diet. The mechanism of action of this diet is ketosis resulting from reduced carbohydrate intake. ESPGHAN is authorized to use the ketogenic diet as an alternative approach to diet therapy for obesity in pediatric practice [23]. The indications for prescribing this diet in children and adolescents are morbid obesity, as well as the presence of complications of obesity (obstructive sleep apnea syndrome, metabolic syndrome, etc.), in which rapid weight loss at the initial stage of treatment is recommended. The duration of the ketogenic diet in children and adolescents should not exceed 10 weeks. The maximum rate of weight loss is noted during the first 2 weeks, and then ranges from 0.5 to 1 kg per week. Patients need regular medical follow-up to monitor adherence to the diet and identify potential side effects. Adherence to the ketogenic diet is accompanied by a high risk of electrolyte imbalance, especially hypokalemia. Possible complications include weakness, orthostatic hypotension, diarrhea or constipation, and cholelithiasis. An adequate drinking regimen is necessary to prevent dehydration. Due to the restriction of fruits, vegetables and dairy products, additional multivitamin intake is recommended, providing 100% of the recommended intake rate [13]. The complete blood count, liver function parameters, serum amylase and albumin levels, and the concentration of ketones in urine should be examined at least once a month [24].

After the end of the diet, carbohydrates are introducing into the diet for several weeks. A number of studies have shown good tolerance for the diet, absence of a pronounced hunger, preservation of a high quality of life. With short-term use, this diet appears to be more effective than the standard hypocaloric diet, which is confirmed by a more significant reduction in body weight, adipose tissue, as well as a decrease in insulin resistance indices [23].

Despite the above advantages of the ketogenic diet, it should be noted that the main indication for its use is pharmacoresistant epilepsy. The number of randomized controlled trials on its isolated efficacy in obese children is currently small. Exclusion from the diet of most fruits, vegetables and cereals, due to the need to sharply limit carbohydrate intake, leads to a deficiency of dietary fiber. It has a negative impact on the gut microbiota and determines the limitation of the duration of use of the diet [6].

Diet with reduced glycemic load

Carbohydrate metabolism disorder with the formation of insulin resistance develops in most obese children. A differentiated approach to the selection of foods containing carbohydrates, taking into account glycemic index, can reduce the load on the insular apparatus and thus improve the clinical course of obesity. This approach categorizes foods into high (≥70), medium (56–69), and low (≤55) glycemic index groups. Reduction of body weight in this variant of the diet is slower than in the ketogenic diet, but is not accompanied by negative effects. A sufficient amount of unsweetened fruits and vegetables determines the feeling of satiety and contributes to a longer adherence to the recommendations [5]. It has been shown that children lose more fat mass on a low glycemic load diet than on a fat-reducing diet. In children aged 6–12 years, the use of such diet results in loss of body weight in a short time. In adolescents 13–18 years of age, a reduced glycemic load diet, in addition to body weight loss and optimizing body composition in the short term, contributes to the maintenance of the achieved values after 1 year [25].

"Food traffic light"

The "traffic light" diet does not fully qualify as an alternative nutritional therapy for obesity in children, as it is intended for long-term use. This approach is part of a program designed for elementary school children and their families that includes family counseling, increased physical activity, and regular counseling by a psychologist. The goal is to preferentially consume foods with low energy value. Products are divided into 3 categories: "green", "yellow" and "red" (Table 3). Low calorie foods (most fruits and vegetables) are considered "green" and recommended for frequent consumption. Moderate energy foods (e.g., cereals) are considered "yellow" and restricted. "Red" high calorie foods are to be severely restricted. The program involves educating the family about

grocery shopping and individual psychological training to support the child's motivation to lose weight [26]. The target group for this nutrition program is obese children aged 6–12 years.

It is shown that the use of the "food traffic light" diet leads to a decrease in body weight in obese children with preservation of the achieved results in the long term (5–10 years follow-up). The effectiveness of the "food traffic light" program depends on the implementation of additional recommendations and family participation in lifestyle changes. In modern foreign recommendations, this approach to nutrition has proven effectiveness and is one of the behavioral strategies for forming a healthy lifestyle in obese children [21].

A universal component of obesity treatment programs is the monitoring of food eaten in the form of a food diary. The diary is kept by the child or parents. Daily physical activity is also noted. Analysis of the food diary is performed both by the pediatrician/nutritionist and parents or patient, especially when the child is adolescence [1].

Despite the availability of various nutritional approaches to the treatment of obesity in children, it is often impossible to follow them for many years. In this regard, the formation of a correct stereotype (pattern) of nutrition, which is widely used in foreign practice, seems relevant. The aim of this approach is to consolidate the stereotype of healthy eating in children and adolescents to ensure optimal eating behavior in further age periods. Recommendations for the formation of a healthy eating pattern as a component of therapy, proposed by the European Society of Pediatric Endocrinologists, include:

- reducing the consumption of fast food;
- reducing the use of added sugars and eliminating sugary drinks;
- reducing the consumption of foods rich in fat, sodium and deeply processed foods;
- consuming whole fruits instead of fruit juice;
- teaching to control portion size;
- reducing saturated fat intake;
- consuming dietary fiber, vegetables and fruits according to national recommendations;
- eating regular meals at specific times;
- identifying situations that encourage overeating [20].

KEY NUTRIENTS IN PEDIATRIC OBESITY

An important aspect of the modern nutritional approach for the treatment of obesity in children is the search for key nutrients, which supplementation allows to control nutritional and metabolic status in this category of patients. Polyunsaturated fatty acids, L-arginine and polyphenols are promising nutrients for inclusion in the diet.

Table 3. Nutritional Recommendations for the Traffic Light Diet

Таблица 3. Рекомендации по питанию для диеты «пищевого светофора»

«Красный» цвет / "Red" color	«Желтый» цвет / "Yellow" color	«Зеленый» цвет / "Green" color
• Фастфуд / Fast food. • Майонез / Mayonnaise. • Плавленый сыр / Process cheese. • Жирная сметана / Full-fat sour cream. • Жирное мясо (свинина, жирная птица) / Fatty meats (pork, fatty poultry). • Копчености / Smoked meats. • Торты и пирожные с кремом / Cakes and pastries with cream. • Дрожжевая выпечка / Yeast baked goods. • Белый хлеб / White bread. • Газированные и сладкие напитки / Carbonated and sugary drinks	• Макароны из твердых сортов пшеницы / Durum wheat pasta. • Каши на воде (кроме манной) / Porridge with water (except semolina). • Выпечка из несладкого слоеного теста / Unsweetened puff pastry. • Отварной картофель / Boiled potatoes. • Нежирное мясо / Lean meat. • Вареная колбаса / Boiled sausage. • Горький шоколад / Dark chocolate. • Пастила, мармелад, зефир / Pastilla, marmelade, zephyr. • Твердый сыр / Hard cheese. • Творог / Cottage cheese. • Сладкие фрукты и сухофрукты / Sweet fruits and dried fruits. • Пряности / Spices. • Кетчуп и соленья / Ketchup and pickles	• Капуста / Cabbage. • Зеленые салаты / Green salads. • Огурцы / Cucumbers. • Томаты / Tomatoes. • Патиссоны / Squash. • Баклажаны / Eggplant. • Морковь / Carrot. • Зелень / Greens. • Яблоки / Apples. • Цитрусовые / Citrus. • Клубника и смородина / Strawberries and currants. • Оливковое масло / Olive oil. • Морепродукты / Seafood. • Отварная рыба / Boiled fish. • Нежирные йогурты / Low-fat yogurts. • Кефир, простокваша / Kefir, curdled milk. • Яйца вкрутую (до 2 штук) / Hard-boiled eggs (up to 2 pieces)

Polyunsaturated fatty acids

Low-fat diet is not recommended in pediatric practice due to the danger of fat deficiency in the body and disruption of normal development and health. At the same time, taking into account the heterogeneity of the fat component, certain positive effects in obesity can be achieved by changing the qualitative composition of fat, in particular, by reducing the level of saturated and increasing unsaturated and polyunsaturated fatty acids (PUFAs).

PUFAs are fatty acids containing at least two double bonds. According to the position of the first double bond relative to the methyl end, PUFA molecules belong to the families ω-3, ω-6, ω-9 and others. The ancestors of PUFA families, ω-3 and ω-6, are essential α-linolenic and linoleic fatty acids, which cannot be synthesized in the human body and must be supplied with food [27].

The main prerequisites for the use of PUFAs to enrich the diets of obese children are: influence on the expression of genes-regulators of carbohydrate and lipid metabolism, regulation of inflammation, regulation of the formation of endocannabinoids (regulators of appetite and energy homeostasis). Dietary enrichment with PUFAs, especially PUFAs of ω-3 family, leads to a decrease in triglyceride synthesis by the liver and release of LDL from the liver into the bloodstream and reduces fat deposition in depots. Reduction of triglyceridaemia and improvement of blood lipoprotein profile serves as a factor in the prevention of cardiovascular complications of obesity. In addition, ω-3 PUFAs inhibit the expression of genes associated with the development of chronic subclinical inflammation accompanying obesity [28].

Actual nutritional studies show that the diet of modern human is dominated by saturated fatty acids to the detriment of PUFAs, and the ratio of ω-6/ω-3 PUFAs is shifted towards the predominance of ω-6 and is 20–30:1 instead of the recommended 5–10:1, It leads to the fact that all metabolic processes in the body occur against the background of inflammation due to the predominance of metabolites of ω-6 PUFAs, which have the most pronounced pro-inflammatory properties [29]. It was noted in the literature, that ω-6 PUFA, namely arachidonic acid, has adipogenic properties associated with the formation of prostacyclin. It stimulates the synthesis of substances necessary for the final stage of adipogenesis, and 2-arachidonoyl-glycerol, the main endogenous cannabinoid, which, binding to the appropriate receptors of the brain, stimulates food intake and fat synthesis. Consequently, excess ω-6 PUFA and high ω-6/ω-3 PUFA ratio in the diet may lead to adipogenic effects [30]. Reduction of adipogenesis can be achieved by reducing the proportion of saturated fatty acids in the diet (no more than 10% of the daily fat requirement) and reducing the ratio of ω-6/ω-3 PUFAs in the diet to the norm of 5–10:1 [31]. The richest source of ω-3 PUFAs is fish and seafood. It is estimated that consumption of fish or seafood 1–2 times a week provides an average daily intake of ω-3 PUFAs at the level of physiologic need for these compounds. The source of ω-6 PUFAs are vegetable oils: sunflower, corn, etc., the content of these compounds is 40–60% of the sum of fatty acids in the product.

L-arginine

Arginine may be considered as one of the key nutrients in obese children. As a precursor to the nitric oxide, amino acid arginine regulates many metabolic processes including fatty acid, glucose, amino acid and protein metabolism by activating signaling pathways and gene expression. Arginine's effects include stimulation of lipolysis and expression of key genes responsible for activating the oxidation of fatty acids to CO2 and water. In addition, arginine regulates the interaction between adipocytes and muscle cells during energy metabolism by acting on cytokine and hormone secretion [32]. Arginine action in skeletal muscles restores insulin sensitivity [33].

There is a lot of researches showing that arginine supplementation may be a new approach to the treatment of obesity and metabolic syndrome. Meta-analysis of randomized placebo-controlled studies (12 studies: 492 participants) showed that short-term (3 to 180 days) arginine administration at a dose of 3 to 24 g/day improves endothelial function and promotes endothelial recovery in case of endothelial dysfunction, including against the background of hyperlipidemia due to high fat intake [34].

At the beginning of the XXI century, it was suggested that arginine promotes the preservation of fat-free mass in the process of body weight loss. Arginine has been shown to be effective in the treatment of abdominal obesity in adults [35].

Nowadays, there are few studies that have examined the effects of arginine in children. However, they confirmed good tolerability of arginine

administration in the pediatric population [36]. Dietary supplementation with L-arginine at a dose of 9 g/day in combination with nutritional therapy and aerobic physical activity in obese adolescents has been shown to be accompanied by stabilization of body muscle mass [37].

A recent study of an arginine product for obese children [38, 39] in addition to a hypocaloric diet found a statistically significant reduction in internal organ fat area and preservation of skeletal muscle mass and active cell mass.

Polyphenols

Polyphenols are minor biologically active compounds of plant origin. They are found in various food products: fruits, vegetables, cereals, nuts, coffee, cocoa, spices, seeds. Depending on the structure of the molecule among them are phenolic acids, stilbenes, flavonoids, lignans. In the literature, there are numerous data on the effect of the consumption of polyphenolic compounds, mainly flavonoids and their subclasses: lignans, on the reduction of excess body weight [40].

The use of polyphenols both in the form of dietary supplements and as part of foods of plant origin can modulate the pathogenetic factors of obesity. Biological effects of polyphenols include inhibition of adipocyte differentiation and transformation of white adipocytes into brown adipocytes, regulation of lipid metabolism, appetite suppression, increase in energy expenditure, and modulation of gut microbiota composition. Polyphenolic compounds (especially resveratrol and quercetin) can affect adenosine monophosphate-activated protein kinase, which triggers the inhibition of fat accumulation, reduces cholesterol synthesis, and modulates inflammatory cytokines [41, 42].

It was shown that the use of catechin contained in green tea extract was accompanied by a decrease in lipid accumulation in the body due to inhibition of differentiation of 3T3-L1 preadipocytes into adipocytes. And administration of epigallocatechin gallate at a dose of 583 mg of catechins per day for 12 weeks caused a decrease in adipose tissue mass and serum levels of cholesterol, low-density lipoproteins [43]. In another study, curcumin was demonstrated to promote the conversion of white adipocytes to brown adipocytes [44]. Green tea polyphenols at a daily dose of 400–600 mg increase antioxidant levels and decrease serum leptin levels, reduce fatty acid absorption and decrease IL-6 and TNF gene expression levels. The ability of polyphenols to reduce high blood pressure has also been proven in clinical studies [45].

CONCLUSION

Thus, nutritional optimization is one of the leading aspects of non-drug therapy of obesity in all age groups. The particular importance of nutrition in children and adolescents is related to the limited options for medical and surgical treatment of obesity at this age. The development of an effective approach to nutritional therapy is complicated by the need to provide children with the energy and nutrients necessary to maintain normal growth and development. The method of choice is an individualized normocaloric diet with sufficient protein content and control of carbohydrate and/or fat content, tailored to the child's food tolerance and taste preferences. Supplementation of key nutrients for nutritional status may be considered a promising therapeutic strategy.

Despite the crucial role of diet therapy in obese patients, it should be taken into account that it is only part of a comprehensive treatment approach that includes a spectrum of non-drug, pharmacologic, and surgical methods. The isolated use of diet for the treatment of obesity is not effective in the long term and should not be recommended to patients as the only method of weight loss.

ADDITIONAL INFORMATION

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

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TYPE 1 DIABETES AND BRONCHIAL ASTHMA IN CHILDREN: INTERRELATION AND MUTUAL INFLUENCE. SCIENTIFIC REVIEW

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Abstract. The aim of this scientific review is to systematize and analyze the literature on the epidemiology, pathogenesis, clinical manifestations, and treatment of children with comorbid pathologies — bronchial asthma combined with type 1 diabetes mellitus — in the context of comorbidity or the diseases' independence/antimorbidity. The study demonstrated that the relationship between type 1 diabetes mellitus (T1DM) and bronchial asthma (BA) is much deeper and more complex than previously thought under the Th1/Th2 paradigm. Allergic and autoimmune diseases are considered comorbid pathologies that are closely interlinked, affecting the onset, sequence of clinical symptoms, nature of control, and specificity of each other's therapy. Scientific data indicate the existence of a common complex polygenic basis for the development of both conditions. Genetic differences may play a crucial role in the relationship between type 1 diabetes and bronchial asthma, but further research in this area is needed. Current understanding of potential pathogenetic and immunological triggers playing key roles in the onset, progression, and treatment of the combined T1DM+BA condition can be conceptualized as a tripartite interaction of genetic factors, environmental conditions, and a unique cytokine profile in these patients. The multifactorial connection should now be considered bidirectional by nature, with each element of this system impacting the others without a clear sequential order. The pathogenesis of the combined pathology (T1DM+BA) is based on immune dysregulation with a cytokine imbalance (a reduction in the number and depletion of reserve capacities of T-reg cells, as well as a defect in the suppressive mechanism of IL-10). This results in the emergence or intensification of the inflammatory process, an imbalance in autoimmunity mechanisms, further disrupting immune homeostasis and leading to the development and progression of symptoms in both BA and T1DM.

Keywords: *children, bronchial asthma, type 1 diabetes mellitus*

САХАРНЫЙ ДИАБЕТ 1-го ТИПА И БРОНХИАЛЬНАЯ АСТМА У ДЕТЕЙ: ВЗАИМОСВЯЗЬ И ВЗАИМОВЛИЯНИЕ. НАУЧНЫЙ ОБЗОР

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Резюме. Цель научного обзора — систематизация и анализ имеющихся в литературе данных по эпидемиологии, патогенезу, клинической картине, а также терапии детей с сочетанной патологией: бронхиальная

астма + сахарный диабет 1-го типа пациентов в контексте коморбидности или самостоятельности/антиморбидности данных заболеваний. В результате проведенного исследования показано, что связь между сахарным диабетом 1-го типа (СД1) и бронхиальной астмой (БА) намного глубже и сложнее, чем существовавшая ранее парадигма Th1/Th2. При этом аллергические и аутоиммунные заболевания являются коморбидной патологией, тесно взаимосвязаны, оказывают влияние на дебют, последовательность возникновения клинических симптомов, характер контроля и особенность терапии друг друга. Научные данные свидетельствуют о существовании общей сложной полигенной основы формирования СД1 и БА. Возможно, именно генетические различия могут иметь решающее значение во взаимоотношениях сахарного диабета 1-го типа и бронхиальной астмы, но исследования в этом направлении должны быть продолжены. И поэтому современное представление о потенциальных патогенетических и иммунологических триггерах, играющих решающую роль в дебюте, течении и терапии сочетания БА+СД1, можно представить в виде тройственного взаимоотношения *генетических факторов, окружающей среды и уникального цитокинового профиля* у данных пациентов. Многофакторную связь в настоящее время следует рассматривать как двунаправленную по своей природе. При этом каждый элемент этой системы влияет на другие без четкого последовательного порядка возникновения. В основе патогенеза сочетанной патологии (СД1+БА) лежит иммунная дисрегуляция с цитокиновым дисбалансом (снижение количества и истощение резервных возможностей T-reg клеток, а также дефект подавляющего механизма IL-10). Следствием этого является появление/усиление воспалительного процесса, разбалансировка механизмов аутоиммунитета, что сопровождается еще большим нарушением иммунного гомеостаза и формированием/прогрессированием симптомов как БА, так и СД1.

Ключевые слова: *дети, бронхиальная астма, сахарный диабет 1-го типа*

INTRODUCTION

The relationship between autoimmune and atopic diseases is a subject of scientific interest and close attention of scientists all over the world, especially in recent decades due to the widespread and steady increase in the number of patients not only with bronchial asthma (BA) but also with type 1 diabetes mellitus (T1DM) [1].

BA is a heterogeneous disease manifested by different phenotypes and characterized by chronic airway inflammation, the presence of respiratory symptoms (wheezing, dyspnea, chest congestion and cough) that vary in time and intensity and manifest with variable airway obstruction [2]. BA occupies the leading place among chronic respiratory diseases in children. Both in Russia and abroad there is not only an increase in children suffering from BA [2, 3], but also a shift of the disease debut to an early age (2–3 years of life). And if in the second half of the XX century, the incidence was higher in children living in more prosperous countries, then recently the trend of BA growth has been registered in developing countries [4]. As it is known, the pathogenesis of BA is quite complex and associated with a complex influence of both *internal* (genetic predisposition to atopy and bronchial hyperresponsiveness, gender, obesity) and *external factors* (food, household — house dust mites, cockroaches; epidermal — animal allergens; fungal allergens, plant pollen and other air pollutants, such as ozone, sulfur and nitrogen dioxides, diesel combustion products, tobacco smoke, active and passive smoking; infectious agents — mainly respiratory viruses; diet — increased consumption of highly processed foods, increased intake of omega-6 polyunsaturated fatty acid and decreased intake of antioxidants in the form of fruits and vegetables and omega-3 polyunsaturated fatty acid in fatty fish; occupational hazards [2, 3, 5–7].

In the pediatric population, in parallel with the increase in allergic respiratory diseases, there has been a significant increase in autoimmune disorders, the main one is T1DM [1]. It is a multifactorial chronic pathology, caused by cell-mediated immune destruction of the pancreas as a result of a complex interaction between genes and environmental factors, when chronic insulitis leads to T-lymphocyte destruction of β-cells with subsequent development of absolute insulin deficiency [8]. In most countries, including the Russian Federation, an increasing incidence of T1DM in childhood is registered. The prevalence of T1DM is 22.9 new cases per year per 100,000 children under 15 years of age [9] and number of such cases is increasing by approximately 3–5% per year [10–12]. In meta-analysis, M. Mobasseri et al. [13] showed not only a steady increase in the incidence of T1DM in the last decade worldwide (the incidence of T1DM was 15 per 100,000 people, and the prevalence was 9.5 per 10,000 people), but also the existence of differences in the incidence of T1DM in children in different geographical regions and ethnic and racial distribution. Very high incidence

(greater than or equal to 20 per 100,000 per year) was in Sardinia, Finland, Sweden, Norway, Portugal, UK, Canada and New Zealand and low incidence (less than 5 per 100,000 per year) was in China, Japan and Rwanda [14]. The incidence of T1DM increased with age, with maximum in children 10–14 years of age [14].

Scientists all over the world have noted that in recent decades there has been a steady increase in the number of patients with a combination of atopic and autoimmune diseases, including BA and T1DM. However, there are few articles devoted to the study of pathogenetic aspects of molecular genetics and cell-receptor mechanisms of its development and manifestation, peculiarities of the clinical debut, interrelation/interaction, comorbidity or antimorbidity of the combined pathology. But this knowledge is quite contradictory (from statistically significant evidence of inverse association between autoimmunity and one or more atopic diseases to confirmation of positive association) [15–18].

At the same time, every attempt to understand this situation raises new and new questions concerning the interaction/interrelation/influence of autoimmune and atopic mechanisms in the genesis of T1DM and BA, since the presence of two such serious chronic diseases in one child requires not only a careful selection of therapy, but, for example, aimed at preventing the formation of complications.

AIM

Therefore, the aim of this review was to systematize the data available in the literature concerning the epidemiology, pathogenesis, clinical features and therapy of patients suffering from the combined pathology of BA and T1DM in the context of comorbidity or independence/antimorbidity of such diseases.

TH1/TH2 PARADIGM

It is well known that BA and T1DM belong to chronic inflammatory diseases. However, the pathogenesis of each nosology is based on the involvement of opposite branches of the adaptive immune system [15, 19], synthesizing different subpopulations of CD4+ T-helper cells of types 1 and 2. Two ways mediate reactions of cellular immune response (Th1) proceeding by the mechanism of chronic inflammation, or reactions of humoral immune response associated with the production of antibodies (Th2). The main cytokines of the Th1 immune response underlying autoimmune pathology are *pro-inflammatory cytokines*: interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), while in Th2 immune response, which leads to IgE-mediated (atopic) diseases (BA), are *anti-inflammatory cytokines*: IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and transforming growth factor-β (TGF-β) [15, 19–21]. The difference in cytokine secretion between Th1- and Th2-immune response cells leads to functional differences, because Th1 cells, producing IFN-γ, activate CD8+ T-lymphocytes and macrophages and promote cellular immunity, while Th2 cells stimulate the synthesis of IgM, IgG1 and IgE and activate eosinophils, contributing to the development of atopy through activation of IL-4 and IL-5 synthesis [22]. At the same time, IL-4 and IL-10, the exclusive products of Th2-immune response, inhibit IL-2-mediated Th1-immune responses and suppress the production of pro-inflammatory cytokines [23]. And therefore, scientists suggested that Th1 cytokines play a direct role in the pathogenesis and progression of T1DM, while Th2 cytokines should provide protection against Th1-mediated destruction of β-islet cells. For this reason, for almost three decades, there has been a hypothesis based on the assumption that diseases mediated by Th1- and Th2-immune responses should be mutually exclusive, because the expansion of Th1 clones in individuals with T1DM should lead to a reduction of Th2 clones, thus preventing the development of atopic diseases and vice versa [24–30]. Consequently, autoimmune (associated with Th1–1) and allergic (associated with Th1-immune response) diseases would be mutually exclusive [29–32].

This concept is supported by a number of comparative studies on epidemiology. It was shown that patients with T1DM have a lower incidence of BA than controls [33]. The authors considered, one of the factors explaining the negative association between T1DM and BA is an increase in the level of glucocorticosteroids with anti-inflammatory effect in patients with BA [34]. Consequently, according to scientists, the presence of T1DM reduces the risk of manifestation of atopic diseases. Also, a retrospective cohort non-comparative study of the incidence of BA in 7230 children with T1DM hospitalized at the Morozov City Children's Clinical Hospital (MCCH) between 2003 and 2012 showed that the incidence of BA in patients with T1DM was 0.86%, which is significantly lower than the population data. This fact may be an indirect

confirmation of the Th1/Th2 concept of immunopathogenesis of T1DM and atopic diseases [35]. M.A. Toska et al. [36] evaluated lung function in 20 children with a combination of T1DM and allergic rhinitis (AR) and in 59 controls suffering only from AR. Scientists found that children with AR had a significant increase in forced expiratory flow rate (by 25 and 75% of forced vital capacity) after bronchodilation compared to the group of children with a combination of T1T1DM and AR. This result may indicate a possible protective role of T1DM associated with AR in the development of BA. In meta-analysis of 25 studies from Europe and North America, C.R. Cardwell et al. [37] described a decreased incidence of BA in children with T1DM (OR 0.82; 95% CI 0.68–0.99; p=0.04). Also in other study, H.O. Mirghani et al. [38] showed a potential protective role of T1DM in relation to the development of atopic dermatitis (AD) (OR 0.69; 95% CI 0.67–0.72). J.P. Krischer et al. [39] found that in children with the first-degree relative who had T1DM, the occurrence of islet cell antibodies (ICA), as the first autoantibodies associated with T1DM, reduced the subsequent risk of BA, AR, and AD, and a presence of autoantibodies to insulin (Anti-insulin IgG) or glutamate decarboxylase (GADA) — atopic dermatitis [39]. Several studies [29–32] have also shown that the occurrence of BA and allergic respiratory symptoms is reduced in patients with T1DM. This protection may extend to siblings of probands without T1DM [25]. But, according to the authors, this, firstly, suggests an effect mediated by a common genetic background, and secondly, by exposure to the same environmental factors during pregnancy or early life [25].

Thus, for more than two decades, the Th1/Th2 paradigm has supported the theory of immune system polarization. Internal and external factors acting together initiate either a Th1-immune response, which through the release of pro-inflammatory cytokines (IFN-γ, IL-2, lymphotoxin-α and others) causes activation of macrophages, increases cellular cytotoxicity and so on, or Th2, which is mediated by anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13, etc.) and leads to the activation of eosinophils as well as induction of antibody formation, including IgE. And thereby determining the balance between two different inflammatory patterns [9].

"HYGIENE HYPOTHESIS" AND OTHER FACTORS

Despite the large number of scientific data and some success in the study of pathogenesis of both T1DM and BA, there is currently opposite data on the interrelated course of these diseases. Among the published works, there are studies both confirming relationship and pointing to genetic, immunologic, and environmental factors contributing to the antimorbidity of the pathologies [41, 42]. A retrospective cohort study was conducted from 1998 to 2011 with use of data from the Taiwan National Health Insurance System. The research included 3,545 children younger than 8 years of age (55.1% girls and 26.5% boys) with T1DM and 14,180 control. It was shown that children with T1DM had a 47% higher incidence of BA (6.49 vs. 4.42 per 1,000 persons, respectively) and an adjusted risk ratio (HR) of 1.34 (95% CI [CI]¼ 1.11–1.62). Meanwhile, patients with T1DM, hospitalized more than twice at emergency department because of diabetes, had a 2-fold higher adjusted risk (HR) of development of BA, which was 38.6 (95% CI 28.5–52.2) versus 17.4 (95% CI 12.9–23.6). Consequently, according to the authors, children with T1DM had significantly higher incidence of bronchial asthma than controls, and the absence of T1DM compensation increased the risk of its formation [43].

M.H. Black et al. [44], as well as Y.T. Hsiao et al. [43], showed a higher prevalence of BA in adolescents with T1DM (10.8%) compared to the general population (8.7%). Also authors found that young people with T1DM, who had the highest number of visits to emergency department or frequent hospitalizations for T1DM, were characterized by a higher risk of development of BA. S. Klamt et al. [45], as well as H. Villa-Nova et al. [46] demonstrated that children with T1DM more often had manifestations of IgE-mediated allergies (allergic rhinitis, urticaria and BA), as well as sensitization to allergens compared to controls without diabetes, which, according to J. Kero et al. may be explained by the coexistence of Th1 and Th2-dependent pathologies. The authors hypothesized a common environmental trigger for both diseases [47], which may influence the susceptibility of patients to BA and T1DM [48].

In the studies, D. Strachan [49], P.I. Pfefferle et al. [50] found that children living with several older siblings, especially in the same bedroom [51], or attending kindergarten before 1 year of age have a lower risk of forming allergic diseases [50] and T1DM [14] than children attending kindergarten over 2 years of age and children from small families. A child's life on a farm, associated with early contact with farm animals, also plays a protective role in the formation of T1DM [52].

According to other authors, the improvement of living conditions in developed countries has led to a decrease in parasitic infections, which may correlate with an increase in the frequency of immune-mediated disorders. At the same time, a number of researchers have pointed out the role of parasitic infections in the formation of autoimmune and atopic pathology in children [53, 54]. They demonstrated that helminths can prevent the development of such diseases by inducing an increase in Th2 cytokines and reducing the secretion of cytokines associated with the Th1/Th17-immune response [55]. Helminths promote the synthesis of gastrointestinal mucosa by synthesis of FhHDM (*Fasciola hepatica*) and *omega-1 (S. mansoni)* [56], which are defense molecules of helminth and possibly play an important role in atopic and autoimmune diseases. Due to the lack of research, the association of atopic and autoimmune diseases with the presence of helminths in the body is controversial.

K.E. Fujimura et al. [57] found that the composition of gut microbiota in infants of the first month of life is crucial for the development of the immune system, so any changes during this period can cause irreversible changes in this. Thus, the microbiota in children at high risk of development T1DM or BA is characterized by common taxonomic features: low phylum biodiversity [18, 58], higher *Bacteroides/Firmicutes* ratio, relative abundance of *Clostridium* and relative deficiency of *Lactobacillus* and *Bifidobacterium* [18, 59]. Many authors believe that this phenomenon may be based on the increased production of short-chain fatty acids (SCFAs) by bacteria (acetate, butyrate, and propionate), as they are involved in the regulation of both innate and adaptive immune systems via the G-protein-coupled receptor (GPR43) [60]. Thus, acetate reduces the number of autoreactive T cells, butyrate promotes the differentiation and activation of Treg cells [61]. Components inhibit the expression of class I genes of the major histocompatibility complex (MHC) and stimulate proteins on B-lymphocytes, promote the differentiation of B cells into plasma cells and memory cells that produce specific IgG and IgA [62]. Meanwhile, acetate and propionate increase insulin sensitivity, and butyrate maintains the integrity of the intestinal epithelium [63]. The findings were confirmed in an experimental study in non-obese mice with T1DM by supplementation with butyrate and acetate, which had a protective effect, reducing the incidence of autoimmune diabetes or delaying its onset [64]. In addition, mice with defective production of GPR43 or SCFAs showed a stronger inflammatory response with high production of pro-inflammatory cytokines after exposure to conventional aeroallergens [65]. However, the mechanism of tolerance is maintained through a complex network of interactions between several cell types (T- and B-lymphocytes, DCs and others). At the same time, excessive migration of DCs can lead to its abnormal activation, imbalance of immune response, which contributes to autoimmune manifestations, infectious and allergic diseases [66]. Chronic inflammation can also induce the formation of neoepitopes that avoid central tolerance and thus promote the formation of autoantigens with massive activation of autoreactive T lymphocytes [67]. At the same time, gut dysbiosis in the presence of reduced microbiota diversity, which is characteristic of many chronic non-infectious diseases, plays a crucial role in tolerance disorders and underlies the genetic predisposition to the development of atopic and autoimmune diseases (*HLA-haplotypes*, genes encoding cytokines or their receptors) [68, 69].

Metsala et al. [70] in nationwide cohort study, included Finnish children under 16 years of age born between January 1, 1981, and December 31, 2008 who had BA (n=81,473) or T1DM (n=9541) by the end of 2009, a 10% random sample from each birth year cohort (n=171,138) was selected as the reference group. Children were identified from the Central Register of Medicines maintained by the Finnish Social Insurance Administration. Authors studied the association between BA and T1DM using a multiple-condition modeling approach to estimate the rate of transition between health and disease from birth. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to represent the change in the rate of transition between both diseases. The authors found that when adjusted for sex and decade of birth, a pre-existing diagnosis of T1DM reduced the risk of subsequent BA by 18% (95% CI 0.69–0.98), and a pre-existing diagnosis of BA increased the risk of subsequent T1DM by 41% (95% CI 1.28–1.54). These results could not be explained by the presence of maternal BA/T1MD or birth-related factors. The authors suggested that the association between these diseases is more complex than previously thought, and its direction may depend on the sequence of disease onset (T1DM in children with BA or BA in children with T1DM) [70].

Also, A.I. Smew et al. [71], in cohort study, investigated the bidirectional association between BA and T1DM and possibility of a shared risk of these diseases. It was made by investigating familial coaggregation model. The study included 1,347,901 children, who were born between January 1, 2001 and December 31, 2013. The data was obtained from several Swedish national registries. All children were born to singleton pregnancies. Cases of BA and T1DM were defined using a combination of diagnoses and drug prescriptions: 121,809 children (9.5%) were diagnosed with BA, 3812 children (0.3%) had T1DM, and 494 children were with a combination of BA and T1DM (0.4% of all BA cases or 13% of all T1DM cases). The authors noted the association between BA and T1DM (OR 1.15; 95% CI 1.05–1.27). Children with BA had increased risk of development of T1DM later in life (OR 1.16; 95% CI 1.06–1.27), but the subsequent risk of development of BA was not significantly different among children with T1DM (OR 0.92; 95% CI 0.75–1.12). Siblings of children with BA were at increased risk of development of T1DM (OR 1.27; 95% CI 1.13–1.42) and vice versa. Results remained positive after controlling for a direct association of one disease with the other. Consequently, the authors' findings suggest the possibility of co-occurrence and coaggregation of BA and T1DM in children, their siblings and, in addition, may indicate common familial factors contributing to the comorbidity of the two diseases [71]. Hyun D. Yun et al. [72], and Zeng et al. [73], in meta-analysis, showed that BA was associated with an increased risk of development of T1DM (OR 2.11; 95% CI 1.43–3.13; p <0.001 and OR 1.15; 95% CI 1.06–1.25, respectively).

J. Xie et al. [74], conducted meta-analysis with use of three databases (PubMed, Embase, and Web of Science) from their inception to February 1, 2021. They studied the presence of bidirectional causality between BA and T1DM based on the calculation of pooled hazard ratios (HR), odds ratio (OR), 95% confidence interval, and full genomic studies (FinnGen). Weighted inverse variance (IVW), weighted median, and MR-Egger methods were used to estimate causal effects. MR-Egger regression and residual sum MR-pleiotropy, an outlier test were performed to assess robustness and horizontal pleiotropy. According to data, BA in children was associated with an increased risk of T1DM (OR 1.30; 95% CI 1.05–1.61; p=0.014), whereas T1DM was not associated with risk of BA (OR 0.98; 95% CI 0.64–1.51; p=0.941; OR 0.84; 95% CI 0.65–1.08; p=0.168). Analysis of variance showed an increased genetic risk of T1DM in children with BA (OR 1.308; 95% CI 1.030–1.661; p=0.028). IVW analysis showed no association between T1DM and genetic risk of BA (OR 1.027; 95% CI 0.970–1.089; p=0.358). Based on their research, the authors concluded that BA in children is a risk factor for the development of T1DM. There is no epidemiologic or genetic evidence of an association of T1DM with the incidence of BA [74].

P. Fsadni et al. [75], compared the registered incidence of T1DM with the prevalence of atopic diseases, and found that T1DM has a positive correlation with both recurrent wheezing and BA. And L.C. Stene et al. [48], analyzing epidemiological data, showed a strong positive association between T1DM and BA and suggested the presence of common environmental factors that may influence the predisposition to both diseases. At the same time, a multicenter case-control study EURODIAB Study 2 Study Group in children proved a negative association of T1DM with BA, BA and rhinoconjunctivitis, respectively [76].

J. Wahlberg et al. [77], included in their study 7208 Swedish children and showed a relationship between the presence of wheezing associated with BA in the first year of life and subsequent appearance of autoantibodies to GADA and antibodies to pancreatic β-cell tyrosine phosphatase (IA-2A) at the age of 2.5 years. In addition, the authors found that allergic rash at multiple sites, recurrent at least three times within 12 months, and symptoms due to sensitization to animal allergens were associated with the risk of IA-2A. Food allergies to egg, cow's milk, fish, nuts/mineral (monovalent or in combination) were associated with risk of formation of GADA and IA-2A. The researchers concluded that allergic symptoms in young children are associated with the appearance of autoantibodies which formed due to T1DM in the first years of life. This fact also confirms the relationship of these diseases [77].

GENETIC HYPOTHESIS

Genetic studies have shown that there are genes involved in the development of both BA and T1DM *(CTLA-4* (lymphocyte-associated protein 4) and *HLA-DQB1 0201/DQB1 0302)*. In this case, N. Taleb et al. [30] found an association, but not statistically significant, between the G-allele in the 49th (A/G) nucleotide of the *CTLA-4* gene and increase in symptoms of BA, as well as a higher risk of development of T1DM [30, 78]. According

to the authors, *CTLA-4* polymorphisms may represent a common genetic risk for both diseases [79]. A study of *HLA-DQB1* alleles showed a higher frequency of *HLA-DQB1* 0201 in children with BA and a higher frequency of *HLA-DQB1* 0301 in healthy people [80]. At the same time, *HLA-DQB1* 0201 carriers and T1DM sufferers were characterized by significantly fewer symptoms of BA compared to patients with T1DM but not carriers of the *HLA-DQB1* 0201 allele. In addition, patients carrying *HLA-DQB1* 0302 tended to have a higher risk of development of symptoms of BA [30]. According to J.C. Barrett et al. [81], the minor allele T of two SNPs (single nucleotide polymorphisms) in *HLA-DQB1* (rs9273349 and rs1063355) can apparently provide protection against both BA and T1DM. In addition, genetic analysis of TLR2 (toll-like receptor 2) showed that the T-allele in SNP rs3804100 is a predisposition allele for both BA and T1DM, and the C-allele is protective for both diseases [82].

M.F. Moffatt et al. [83] identified 9 regions with 10 SNPs associated with BA in a whole-genome study, among which the *ORLMD3/GSDMB* region was the only HLA antigen region common to both BA that began in childhood and T1DM [81, 83]. In the *ORLMD3/GSDMB* region, SNPs rs2305480 and rs3894194, associated with atopy, were also found to be associated with T1DM [83]. M.T. Heinonen et al. [84] in population-based association studies on T1DM and BA/allergic sensitization evaluated the role of *GIMAP4* and *GIMAP5* (GTPase of the immunity-associated protein) polymorphisms and found, that SNP *GIMAP5* (rs6965571) was directly associated with increased risk of both BA and allergic sensitization, but inversely associated with T1DM. SNP *GIMAP4* (rs13222905) was associated only with BA and allergic sensitization. At the same time, the study of Das Sudipta et al. [85] showed that chromosome 17q21 contains a cluster of genes, including *ORMDL3* and *GSDMB*, which are closely associated with both BA and type T1DM. An *ORMDL3* is located in the endoplasmic reticulum and regulates sphingolipids, metalloproteinases, remodeling genes and chemokines, as well as IL-6. An *GSDMB* is one of four members of the *GSDM* family (*GSDMA, GSDMB, GSDMC* and *GSDMD*) and responsible for the expression of TGF-β1, which is involved in the pathogenesis of BA. However, in the study, included 150 children with T1DM and 158 with BA, the authors found no differences in *IL-12R1* and *IL-12R2* gene polymorphisms in both groups of children with such diseases and in comparison to controls [1].

CONCEPT "IMMUNE DYSREGULATION"

Studies conducted in the late XX and early XXI century showed that cytokines of both Th1- and Th2-immune response, which actively interact in the destruction of β-islet cells, are involved in the formation of T1DM. At the same time, the morphology of pancreatic lesions is different [86]. Meanwhile, Th1 pancreatic lesions in T1DM include focal limited insulitis consisting mainly of CD8+ and CD4+ T cells. And β-islet cells die by apoptosis, preserving the surrounding exocrine tissue. Th2 lesions consist mainly of eosinophils, macrophages and fibroblasts. And β-islets die as the result of necrosis. This results in the accumulation of fibroblasts, formation of extensive extracellular matrix and adipose tissue, which leads to tissue necrosis. In addition, macrophages infiltrating islets of Langerhans can secrete pro-inflammatory cytokines IL-1α, IL-1β, TNF-α, and various chemokines that promote the migration of dendritic cells, macrophages, and T lymphocytes [56, 80, 87]. It is often combined with increased levels of IL-2 in plasma [80] and its circulating receptor (CD25) in T1DM patients [56]. The kinetics of β-cell destruction also differ depending on the cytokines of the Th1/Th2-immune response: Th1 lesions are faster, more aggressive and persist for longer periods of time compared to Th2 lesions [22]. Consequently, Th2 lymphocytes and mediators are also actively involved in the pathogenesis of T1DM by facilitating infiltration by pancreatic mononuclear cells and accelerating the destruction of β-islet cells, which suggested, that T1DM is a Th1+ Th2-mediated disease [86, 88]. The progression of T1DM from insulitis (pancreatic mononuclear cell infiltration) to overt hyperglycemia is under the control of the Th1 and Th2 immune response and its respective cytokines [22].

Studies on animal models and people with T1DM confirm the direct role of Th1-lymphocytes and produced cytokines in the pathogenesis and progression of the disease, destruction of β-cells as a result of Th1-induced insulitis. IFN-γ and other cytokines act mainly at the level of activation of macrophages and CD8+ T-lymphocytes, increasing β-cell infiltration and thus accelerating its destruction through the release of preformed, *de novo* synthesized cytokines/chemokines and other mediators (nitric oxide, oxygen radicals, serinesterases…) [89]. In addition, cytokines of the Th1-immune response can induce activation and expansion of autoreactive T cells, as well as suppress the production of soluble cytokine an-

tagonists, including the IL-1 receptor antagonist. In turn, by enhancing β-cell destruction, it can lead to stimulation of IL-1 production by macrophages and significant increase in the expression of IL-2 and other Th1 cytokines [22]. At the same time, the predominance of Th1 cytokines in β-islet cell infiltrates in female but not male NOD mice (with genetically predetermined T1DM formation) has been described as a major predisposing factor for the development of anti-β-cell immunity and subsequent T1DM formation in females but not in males [22]. Consequently, the authors hypothesized that T1DM could be eliminated either by induction of the expression of cytokine of the Th2-immune response or by treating T1DM patients with drugs based on them (IL-4 and IL-10).

Recent studies more often show the possibility of common pathogenetic pathways in the formation of BA and T1DM, which may be based on *immune dysregulation* [9, 90]. For example, in evaluating the immunologic response in children with autoimmune/atopic diseases, it was shown that lipopolysaccharide (LPS)-stimulated peripheral blood mononuclears *in vitro* express a unique pattern of cytokines with a combination of both Th1 and Th2 immune response activity. Higher serum levels of IL-12 and IL-18 were found in children with a combination of BA and T1DM compared to controls. Moreover, IL-12 levels were lower in patients with both diseases compared to children with only one disease [91, 92]. The authors believe that this phenomenon is based on the depletion of mononuclear cells, which cannot increase IL-12 production. The IL-18/IL-12 ratio in serum *in vivo* was also significantly higher in children with a combination of BA and T1DM compared to patients with BA alone [91]. Meanwhile, IL-18 is a key pro-inflammatory cytokine produced by dendritic cells (DC), T- and B-lymphocytes, and macrophages. It is pleiotropic and interacts with a variety of cells. Its elevation is associated with exacerbation of BA [93]. IL-12 is also produced by DC, B cells and macrophages, but the main cellular targets are T lymphocytes and NK cells [87]. In the pathogenesis of T1DM, IL-12 and IL-18 can enhance the cytotoxic activity of T lymphocytes and NK cells, leading to impaired *immunoregulation* through alteration of T-reg cell activity [94].

HYPOTHESIS ON THE ROLE OF T-REG CELLS

The hypothesis of T-reg cell overstimulation may be a promising hypothesis in studying the pathogenesis of T1DM+BA: patients with T1DM and allergy have higher levels of inflammatory cytokines compared to children with only one disease. At the same time, high cytokine levels persist despite hypersecretion of anti-inflammatory IL-10, suggesting functional depletion of T-reg cells [9, 95].

T-regs express P3 protein identified as a transcription factor essential for development and its function (forkhead box, FOXP3). Also T-regs are known to maintain immune homeostasis and prevent autoimmunity, playing an important role in formation of *immune tolerance to own tissues* [96], regulation of host-commensal microflora interactions, and tissue repair. The deficiency and/or dysfunction triggers autoimmune reactions and inflammation [97]. Immunosuppression mediated by T-reg cells can be provided by contact-dependent suppressor mechanisms, inhibitory receptors (CTLA-4, LAG3, galectin-1) or through perforin and granzyme, B-dependent cytotoxic killing of target cells [98]. In addition, T-reg cells can mediate contact-independent suppression by acting through IL-2 (T-reg cell-associated CD25) or by producing inhibitory cytokines such as IL-10, TGF-β, and IL-35 [99]. In addition to general suppressive activity, T-reg cells can additionally differentiate in the periphery and specifically control Th1-, Th2-, Th17-, or T follicular helper (Tfh) immune responses by acquiring the transcription program of the specific effector cells they suppress (T-bet, IRF4, STAT3, or Bcl-6, respectively) [100].

T-reg cells support a balanced adaptive immune response, protecting tissues both directly by repairing through the production of amphiregulin and indirectly by limiting tissue damage with suppressing the inflammatory response [97]. T-reg cells also protect against allergic diseases, transplant rejection, atherosclerosis, and control metabolic disorders [101]. Congenital genetic defects affecting the number and/or function of T-reg cells disrupt immune homeostasis, shifting the balance towards autoimmunity, lymphoproliferation, allergic dysregulation and ongoing lymphocytic infiltration of various organs, including the pancreas, resulting in disease progression. The spectrum of manifestations of T-reg cell defect may vary from mild allergic or autoimmune diseases to lethal outcomes of immune regulation. Thus, mutation of IL-2Rα/STAT5b and CTLA4/LRBA disrupts the homeostasis of the IL-2R-STAT5 signaling pathway and, consequently, the function of T-reg cells. The IL-2 receptor is known to consist of three subunits: α (CD25), β (CD122) and γ (CD132). CD25 binds IL-2 and is constitutively expressed in large numbers

by T-reg cells. Its deficiency impairs the suppressor function and metabolic activity of the latter due to its defective production of IL-10, as well as inability to bind and/or decreased sensitivity of CD25-deficient T-reg cells to IL-2 [102]. This leads to the development of both autoimmune disorders (alopecia, diabetes mellitus, thyroiditis, autoimmune hemolytic anemia, etc.): chronic eczema, enteropathy, lymphoproliferation, and immunodeficiency with recurrent infections caused mainly by herpes viruses [103–105].

It has also been found that children with the combination of BA and T1DM have increased spontaneous production of INF-γ, TNF-α and IL-10 by peripheral blood mononuclear cells (compared to the controls and patients with only one disease) [92]. Meanwhile, it is well known that IL-10 acts directly on Th2 cells. Its specific function is to prevent excessive inflammatory response, inhibit the activity of Th2-immune response and Th17-mediated reactions [106, 107]. The persistence of high levels of pro-inflammatory cytokines despite hypersecretion of anti-inflammatory group (IL-10) in patients with the combination of T1DM and BA [108] may indicate a deficit of regulatory mechanisms of the inflammatory response, its depletion and the inability of T-reg cells to additionally increase cytokine production [92]. This pattern characterized by *"depletion" of T-reg cells* may also be caused by a defect in TCD4+ inhibition, IL-10, HLA gene polymorphisms and CTLA-4 defects in combination with environmental triggers. *Consequently, a defect in IL-10 suppressive mechanism in patients with combined T1DM+BA may contribute to the development/progression of both atopic and autoimmune diseases* [109].

A number of authors have shown that in patients with combined T1DM+BA, T-reg and Th-17 can differentiate independently from Th1 and Th2 cells [110, 111]. At the same time, experimental studies using laboratory animals have established that in NOD model mice there may be an increase in Th2-mediated reactions and the development of experimental allergic asthma through the activation of CD1d-dependent NK cells. Its consequence is eosinophilia and the development of allergic inflammation. This suggests that autoimmune T1DM through activation of relevant cytokines may enhance the Th2-mediated immune response underlying the development of BA [112]. In mice with knockout of the gene encoding the IL-4 molecule, cytotoxic reactions mediated by Th1-lymphocytes may also be impaired. At the same time, knockout of *INF-γ* gene in NOD mice does not prevent T1DM [116, 113]. In addition, several studies have identified a special population of ILC (Helper innate lymphoid cells) that play a fundamental role in the early immune response. Thus, ILC2 participate in allergic reactions by activating the Th2 response, which contributes to an increase in the number of T-reg cells producing IL-10, and IL-C1, which initiates the synthesis of *INF-γ*. It seems to play a key role in the pathogenesis of inflammation in autoimmune diseases, including T1DM [9].

EFFECT OF T1DM+BA ON DISEASE CONTROL

T. Hörtenhuber et al. [114] conducted a prospective multicenter observational cohort study, based on the DPV register (German-Austrian initiative — Diabetes-Patienten-Verlaufsdokumentation) and included 51 926 patients with T1DM under 20 years of age. The prevalence of BA in young patients with T1DM in Austria and Germany was studied, as well as its impact on metabolic control. Among all patients included in the study, 1755 (3.4%) had a combination of T1DM and BA. These patients were more often male (61% vs. 52%, p <0.01) and had a reduced height standard deviation (SDS) (–0.002±1.04 vs. 0.085±1.02, p <0.01) and increased body mass index (BMI)-SDS (0.31±0.89 vs. 0.28±0.89, p=0.04). The authors demonstrated that patients with combined T1DM+BA required higher doses of insulin to control T1DM (0.88±0.3 vs. 0.84±0.3 U/kg, p <0.01, respectively) and experienced more severe hypoglycemia (4.5 [4.2; 4.8] vs. 3.2 [3.2; 3.3] cases/100 persons per year, p <0.01). Glycosylated hemoglobin A1c (HbA1c) levels in patients with T1DM did not differ between patients with and without BA. However, differences were found depending on the therapy received by patients with BA (corticosteroids vs. leukotriene receptor antagonists, corticosteroids vs. sympathomimetics). Thus, those who was taking sympathomimetics had higher HbA1c value compared to the group taking other drugs. The authors suggested an anti-inflammatory effect of anti-asthmatic treatment, emphasizing the complex relationship between lung function, body mass index and glycemic control in children with T1DM. The high insulin requirement, they suggested, could be explained by additional stress, less physical activity and, therefore, slightly higher insulin resistance caused by inflammation, which may be related to both BA and/ or medications, primarily inhaled glucocorticosteroids (IGCS) and β_2-agonists. However, no effect of asthma

medications on metabolic control of T1DM or body mass index has been found [114]. According to J. Metsälä et al. [115], the use of some antiasthmatic drugs (IHCS, β_2-agonists) can be potentially associated with the risk of T1DM development, relative refractoriness of T1DM patients to BA due to its increased level of glucocorticosteroids with anti-inflammatory effect [34].

F. Ahmadizar et al. [116], used in their research Dutch PHARMO patient registration system, including children and adolescents under 19 years of age who received at least 2 insulin prescriptions between 1999 and 2009 (main group, n=915). The use of asthma medications and occurrence of BA exacerbations during 5 years before and after the onset of T1DM was studied. Control group consisted of 3590 patients of the same age and sex. The analysis showed that the 5-year prevalence of the use of medication for BA in patients with T1DM after its debut was significantly higher than in controls (23.2% vs. 18.3%, respectively). There was no statistically significant difference between groups in the use of specific medications for treatment of BA, with the exception of short-acting M-cholinolytics, which were significantly more frequently used in the group of children with combined T1DM+BA compared with controls (5.5% and 0.62%, respectively). Consequently, the authors believe that T1DM is associated with a statistically significant higher use of antiasthmatic medications after the onset of type 1 diabetes mellitus, especially in the first year after the onset of the disease [116]. Children with T1DM and treated for BA had significantly fewer episodes of hypoglycemia and better glycemic control compared with children with only T1DM. Perhaps, the authors believe, the drugs used for treatment of BA, particularly β_2-agonists, have therapeutic potential to reduce hypoglycemia and contribute to improved glycemic control [116]. The authors collected data on 226 children, of whom 27 (12%) were being treated for BA. Only 11 (out of 27) children were taking their prescribed inhaled glucocorticosteroids. But all children were taking β_2-agonists at least once a week. At the same time, the frequency of hypoglycemia in children with T1DM and treated for BA decreased by 20%. In children with T1DM and treated for BA, 52% reported an episode of hypoglycemia in the previous three months, compared with 72% of children who had T1DM only. There were no differences in the proportion of children with nocturnal or severe hypoglycemia. Although not significant, but children with the combination of BA+T1DM had better overall control compared to children with T1DM alone (HbA1c 8.8%, HbA1c 9.3%, respectively). T.D. Wu et al. [117], M.H. Black et al. [44] also found a correlation between T1DM and BA and demonstrated a higher rate of BA in children and adolescents with T1DM. Scientists also demonstrated an association between concomitant BA, poor glycemic control in patients with T1DM (HbA1c: asthma + T1DM: 7.77±0.26% (61.4±2.0 mmol/mol) vs T1DM alone: 7.49±0.2% (58.4±1.5 mmol/mol), p=0.034), HbA1c levels and exacerbation of BA in patients, especially if BA was untreated, i.e. patient did not receive baseline therapy [44]. Similar data on the higher prevalence of BA in children with T1DM and poor glycemic control affecting the course of BA were shown in the study of Hsiao et al. [43] and H. Villa-Nova et al. [46]. In the work of G. Yang et al. [78] it was also reported about the negative association between HbA1c and exacerbation of BA in 47,606 adult patients in the UK. It was also found that perhaps these two diseases can influence the rate of achieving control of each other.

CONCLUSION

Thus, modern epidemiological studies show that the relationship between type 1 diabetes mellitus and bronchial asthma is much deeper and more complex than the existing Th1/Th2 paradigm. Allergic and autoimmune diseases are comorbid pathologies, which are closely interrelated, and affect the onset, sequence of clinical symptoms, pattern of control, and characteristics of each other's therapy. Scientific data indicate the existence of a common complex polygenic basis for the formation of T1Dm and BA. At the same time, it is possible that the genetic differences discovered in the study of patients with a combination of BA + T1DM may be of decisive importance in the relationship between type 1 diabetes mellitus and bronchial asthma.

However, research in this direction should also be continued. The current understanding of potential pathogenetic and immunological triggers that play a decisive role in the onset, course and therapy of BA+T1DM combination can be represented as a triple relationship between *genetic environmental factors and unique cytokine profile in these patients*. The multifactorial relationship should currently be considered as bidirectional in nature, given that each element of this system affects others without a clear sequential order of occurrence. At the same time, pathogenesis

of combined pathology (T1DM+BA) is based on *immune dysregulation with cytokine imbalance (decrease in number and depletion of the reserve capacity of T-reg cells, as well as defect in the suppressive mechanism of IL-10)*. The consequence of this is appearance/intensification of inflammatory process, imbalance of autoimmunity mechanisms, which is accompanied by an even greater disruption of immune homeostasis and formation/progression of symptoms of both BA and T1DM.

That is why physicians should be aware of possible coexistence of autoimmune and atopic/allergic diseases (BA+T1DM), complex mutual influence on each other's onset, common pathogenetic mechanisms of temporal connection, influence on the course and pattern of disease control, as well as the specifics of therapy. It is needed to improve management of patients, increase their quality of life and form a favorable prognosis.

ADDITIONAL INFORMATION

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

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MODERN APPROACHES TO THE INTRODUCTION OF SUPPLEMENTARY FEEDING TO NEWBORNS AND CHILDREN OF THE FIRST YEAR OF LIFE. HOW RIGHT

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Abstract. Over the past decades, under the auspices of the World Health Organization, a lot of work has been done in all countries of the world to support breastfeeding among medical institutions and public organizations. The importance of the formation of a dominant lactation and the provision of professional assistance to a nursing woman is determined. These measures allow you to resolve temporary difficulties and maintain long-term breastfeeding. If there are objective reasons for additional feeding of the child, the appointment of infant formula should be justified and personalized.

Keywords: *newborns, breastfeeding, supplementary feeding, infant formula*

СОВРЕМЕННЫЕ ПОДХОДЫ К ВВЕДЕНИЮ ДОКОРМА НОВОРОЖДЕННЫМ И ДЕТЯМ ПЕРВОГО ГОДА ЖИЗНИ. КАК ПРАВИЛЬНО

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Резюме. На протяжении последних десятилетий под эгидой Всемирной организации здравоохранения во всех странах мира ведется большая работа по поддержке грудного вскармливания среди медицинских учреждений и общественных организаций. Определена важность формирования доминанты лактации и оказания профессиональной помощи кормящей женщине. Данные мероприятия позволяют разрешить временные сложности и сохранить длительное грудное вскармливание. При наличии объективных причин для докорма ребенка назначение детских молочных смесей должно быть обоснованным и персонифицированным.

Ключевые слова: *новорожденные, грудное вскармливание, докорм, детские молочные смеси*

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INTRODUCTION

The problem of nutrition of children of the first year of life is particularly relevant in the modern pediatrics [1, 2].

Increasing the prevalence of breastfeeding (BF) is a target indicator of population health indicators. Modern science defines breastfeeding as the most important postnatal factor of long-term metabolic programming and a factor of protection against "civilization's diseases" in later life [3, 4]. Breast milk (BM) is recognized as the normative standard in infant nutrition [5, 6].

Timing of breastfeeding and type of feeding are key aspects in shaping a healthy generation in the future. The task of all obstetric institutions is to provide timely and professional medical care for mother and child, as well as support breastfeeding, including the organization of optimal feeding for newborns who cannot be breastfed [7].

It should be noted that in recent years there has been data on the not necessarily prescription of formula feeding (FF) in obstetric centers. Thus, according to foreign studies, about half of newborn premature infants received supplementary feeding in the early neonatal period. In more than half of these cases, there were no objective medical indications for the administration of supplementary feeding. These data should be in the centre of attention because the administration of supplementary feeding, regardless of the amount of formula in the first 48 hours, sharply reduces the readiness for breastfeeding in the subsequent period [8].

In Russia, the practice of prescribing FF to healthy newborns without clear justification also occurs at the maternity hospital stage. The prescription of FF in obstetric institutions should be considered as part of therapeutic measures [9].

The association of early introduction of infant formula feeding with the risk of infectious diseases and increased cases of food allergy has been determined [10, 11]. Artificial formula feeding increases the risk of metabolic syndrome, type 1 diabetes mellitus, and cardiovascular diseases [12–14].

A World Health Organisation meta-analysis showed an association between breastfeeding and a low prevalence of overweight or obesity in later life. Perhaps one mechanism for this protective effect is related to protein intake and energy metabolism, which are lower in children who receive breast milk compared to those fed cow's milk [13, 14].

Based on the results of scientific studies, it has been suggested that the development of cardiovascular diseases is programmed in infancy, and a possible reason for the development of pathology is the lack of breastfeeding in the first year of life [13, 14].

Data from epidemiological scientific studies have shown a correlation between cow's milk consumption and the incidence of type 1 diabetes mellitus (DM). It is now suggested that the introduction of infant formula into the diet of children during the first months of life is a trigger that may provoke the development of type 1 DM [15, 16].

Administration of supplementary feeding in obstetric institutions: in the form of mixtures based on cow's milk proteins increases the risk of developing allergy to these proteins by 7 times [17]. It has been established that even a single use of formula leads to an increased risk of allergy development regardless of the amount of formula [18].

There is strong evidence on the role of the gut microbiota in the development of food allergy. Gut microbiota is involved in the formation of oral tolerance. Altered gastrointestinal flora is one of the links in the pathogenesis of a food allergy. There is an evidence that the addition of formulas affects the composition of gut microbiota of the child. The result of this effect is a decrease in the number of bifido- and lactobacilli necessary for competition with opportunistic microorganisms, for the production of short-chain fatty acids and, most importantly, for the stimulation of mucosal immunity [10, 19, 20].

The influence of breastfeeding on the formation of child behaviour and intelligence has been proven. Numerous mechanisms of this influence have been described. The concept of the microbiota-gut-brain axis deserves special attention [21, 22].

Breastfeeding contributes to optimal physical and psychological health and enhances the child's mental and cognitive abilities [23, 24]. A well-known large-scale prospective study found a direct correlation between the duration of breastfeeding during the first year of life, speech development and intellectual ability [23, 25].

It should be noted that not all mothers are able to breastfeed after birth, and not all children are able to breastfeed.

In the Russian Federation, the absolute contraindications for breastfeeding a child from the mother's side are: HIV infection, acute mental disorders, particularly dangerous infections, open form of tuberculosis, carrier of T-lymphotropic virus, treatment with cytostatic and radioactive drugs. The presence of a number of congenital metabolic diseases in children are absolute contraindications to breastfeeding [26, 27].

The awareness of a lactating woman about the occurrence of lactation crises is important for the preservation and maintenance of lactation. It is known that lactation crises occur 3–4 weeks after delivery, in the 3–4th and 7–8th months. The duration of lactation crises is 3–5 days. As a rule, already after 6–8 days more milk is being produced.

During this period of life, it is recommended to frequently apply the baby to the breast, adequate rest, plenty of warm drink, contrast shower on the area of the mammary glands before feeding, light massage of the mammary gland. A positive attitude of the mother and orientation of all family members to support breastfeeding are important, which will help to avoid unjustified transfer of the child to formula feeding [26, 28].

SUPPLEMENTARY FEEDING

The program for optimising infant feeding in the first year of life provides clear recommendations on the introduction of supplementary feeding in newborns and children in the first year of life [26]. When introducing supplementary feeding in the neonatal period, the physician should first of all be guided by the initial weight loss of the child, which normally should not exceed 10% by the third day [29].

The causes of pathological loss of initial body mass on the part of both mother and child (e.g. hypogalactia, anatomical features of the mammary gland, dysphagia, newborn depression syndrome) should also be taken into account.

The protocol of the International Academy of Breastfeeding Medicine emphasises that the first choice of supplementary feeding is decanted mother's milk, donor milk and, only in exceptional cases, infant formula. At the same time, mixtures based on partial protein hydrolysis are the most preferable [30].

It has been established that if supplementary feeding is necessary for a child from 2–3 days of life (loss of 5–6% of body mass 1 day after birth, 7–8% — after 2 days), supplementary feeding in the amount of 10 ml does not affect lactation [31]. In case of ≥10% body mass loss, the amount of supplementary feeding per feeding can be at least 20 ml [32].

On the 1st September 2021, new sanitary and epidemiological rules and regulations SanPiN 3.3686–21 came into effect, according to which the decanted milk of the mother can be used for delayed feeding of the child without subjecting breast milk to special treatment [33].

In 2014, the Scientific Centre for Child Health of the Russian Ministry of Health opened the first donor breast milk bank in the Russian Federation (RF), and then two more breast milk banks were opened (in Ufa and Chelyabinsk) [33].

Another negative aspect of early introduction of supplementary feeding is the decrease in the prevalence and duration of breastfeeding. A systematic review and meta-analysis of 9 prospective studies on the effect of introducing breastmilk substitutes to newborns between 4 days and 4 weeks postpartum on the results of breastfeeding duration showed that this practice is a statistically significant risk factor for shorter breastfeeding duration [34].

According to the Programme for the Optimisation of Infant Feeding in the First Year of Life, insufficient weight gain in the first month of life is the basis for the introduction of supplementary feeding (a gain of less than 400 g in the first month of life is pathological). Children with weight gain for the first month of life in the range from 400 to 600 g, require an individual approach. This allows timely prescription of measures aimed at stimulating lactation and, if necessary, supplementation with infant formula [26, 35].

A rising weight curve centred on standardised growth scales is used to assess and correct any supplementary feeding interventions. Check-weighing can be performed either weekly or daily, depending on the achievement of optimal weight gain (26–30 g/day should be considered normal) [26, 36].

The approximate normal weekly weight gain in the first 3 months of life is 180–200 g per week, and 120–130 g per week at the age of 3–6 months [26]. Control weights are not an objective indication of lactation adequacy and allow to estimate only the amount of breast milk received by the child.

It is necessary to take into account the degree of morphofunctional maturity of the child, features of his physical development, allergological anamnesis, and the presence of functional disorders during choosing a product for supplementary feeding [37]. An important criterion for the correct choice of an infant formula is its good tolerability: an absence of dyspeptic disorders and allergic rashes.

There is no convincing evidence on the advantages of any of the used methods of supplementary feeding, as well as the presence of risks in their use. A baby can be fed in different ways, either from a bottle or from a cup/spoon. In each case, the doctor makes a decision depending on the individual characteristics of the child and the mother's preferences [26].

It is necessary to strive to ensure that infant formula feeding is temporary, administered in a limited amount, carried out against the background

of lactation stimulation and cancelled in a timely manner if the child has stable (over several days) weight gain of at least 20–30 g/day [26].

CONCLUSION

The introduction of supplementary feeding or complete conversion of a child to formula feeding should be strictly justified and carried out only when the need to introduce formula into the child's diet is objective, and the entire arsenal of means aimed at stimulating lactation has proved ineffective. None, even the most modern formula can serve as a full-fledged substitute for mother's milk [37].

An effective measure to support lactation in the mother and to maintain successful breastfeeding in case of inability to breastfeed is feeding the child with decanted breast milk. The use of decanted breast milk without heat treatment maximises the preservation of its biological value. The existing developed and approved recommendations on the organisation of individual breast milk banking in children's medical institutions and at home will certainly contribute to increasing the prevalence of breastfeeding in the Russian Federation [33]. Only the joint work of medical and public organisations will make it possible to maximise the implementation of the program to optimise the breastfeeding of children in the first year of life [38].

ADDITIONAL INFORMATION

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

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

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THE UNIQUENESS OF THE COMPOSITION OF GOAT'S MILK AND THE ADVANTAGES OF USING FORMULAS BASED ON IT IN INFANTS DEPRIVED OF BREAST MILK

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Abstract. The article presents a review of the scientific literature on the peculiarities of the composition of goat's milk. It is noted that whole milk of any farm animals, including goats, is not recommended for use by infants, since their composition does not correspond to breast milk and the body of infants is not capable of adequate digestion and assimilation of phylogenetically unsupported food. It is reflected that the use of innovative technologies in the production of adapted dairy formulas based on goat's milk for infants allows you to preserve all the natural valuable components of raw materials. Clinical studies confirming the effectiveness of using starter formulas based on goat's milk are presented.

Keywords: *breast milk, cow's milk, goat's milk, aS1-casein, aS2-casein, β-casein, β-casomorphin, oligosaccharide, adapted milk formula*

УНИКАЛЬНОСТЬ СОСТАВА КОЗЬЕГО МОЛОКА И ПРЕИМУЩЕСТВА ИСПОЛЬЗОВАНИЯ ФОРМУЛ НА ЕГО ОСНОВЕ У МЛАДЕНЦЕВ, ЛИШЕННЫХ ГРУДНОГО МОЛОКА

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Резюме. В статье представлен обзор научной литературы по особенностям состава козьего молока. Отмечено, что цельное молоко любых сельскохозяйственных животных, в том числе и коз, не рекомендовано для употребления детьми грудного возраста, так как их состав не соответствует грудному молоку и организм младенцев не способен к адекватному перевариванию и усвоению филогенетически не предусмотренной пищи. Отражено, что применение инновационных технологий при производстве адаптированных молочных формул на основе козьего молока для младенцев позволяет сохранить все естественные ценные компоненты сырья. Приведены клинические исследования, подтверждающие эффективность использования стартовых формул на основе козьего молока.

Ключевые слова: *грудное молоко, коровье молоко, козье молоко, aS1-казеин, aS2-казеин, β-казеин, β-казоморфин, олигосахара, адаптированная молочная формула*

INTRODUCTION

A complete, properly organised diet can have a protective long-term effect on human health. This is especially relevant for the growing organism, since the transition to lactotrophic nutrition triggers significant processes in it: the formation of the gut microbiome, epithelial barrier, immune and central nervous systems [1].

Despite the widespread use of cow's milk and products prepared on its basis in the nutrition of children and adults, goat's milk (GM) has attracted and continues to attract special interest of the peoples of different countries of the world for many centuries.

Traditionally, GM was prescribed in Ayurvedic practice (Ayurveda is the art of healthy lifestyle, in which all harmful environmental influences are powerless before perfect health) as a medicine. Abu Ali ibn Sina (Avicenna) wrote about its usefulness, stating that it preserves health and mental clarity. Hippocrates used the healing properties of this product to treat lung and stomach diseases.

In the Middle Ages, cheese made from GM was widely used to treat children with rickets.

In the early twentieth century, the trigger for the study of the beneficial qualities and composition of GM was the observation of infants who did not receive mother's milk. The mortality rate of children whose diets used goat's milk instead of breast milk (BM) was significantly lower than among those fed cow's milk.

In 1900 Paris Academy of Medical Sciences officially recognised GM as a highly dietary product and recommended it for the nutrition of children and people with poor health. In Russia children's doctor and nutritionist V.N. Zhuk, author of the popular book 'Mother and Child', was an active propagandist of GM. With his active support and participation, a farm was organised in the suburbs of St. Petersburg to breed a special species of goat, brought by special order of the government from Switzerland [2].

Currently, the benefits of GM consumption for the human body are actively discussed, including hypoallergenicity, improvement of gastrointestinal disorders, growth rate, bone mineral density, blood serum levels of cholesterol, calcium, vitamin A, thiamine, riboflavin, niacin and others. However, most claims about the benefits of GM are based on unofficial data that are used in industry promotional materials and in the media [3].

For example, one of the main characteristics of GM that has contributed to its appeal as an alternative to cow's milk is its lower allergenicity. Thus, to avoid consuming cow's milk in children with intolerance, families often switch to goat's milk. Until the 1990s, there were sporadic studies indicating its weak sensitisation to cow's milk protein allergy (CMPA) [4, 5].

CMPA is the most common food allergy in early childhood, while in adults the remission rate to this protein is 85–90% [6]. In a review published in J. Dairy Sci (1980) it was noted that in many cases the clinical picture of CMPA did not improve when patients were transferred to GM [7].

C. Ballabio et al. (2011) examined individual milk samples from 25 goats with different genotypes of αS1-CN (the largest of the three subfractions of α-casein) by SDS-PAGE and immunoblotting (IB) using monoclonal antibodies specific to bovine α-casein (α-CN) and sera from children allergic to cow's milk and showed that GM sensitisation is a function of the αS1-CN genetic polymorphism. Lower reactivity was observed for samples with αS1-CN null genotypes (0101 or 01F). This work confirmed that caution should be exercised before offering GM to patients with CMPA as an alternative product [8].

The same conclusion was reached by M. Lisson et al. (2014), who indicated that although genetic variants of ruminant caseins differ in their allergenicity, they are highly homologous (>80–90%) and have similar structural, functional and biological properties. For example, the sequences of αs1-, αs2- and β-caseins of cow, goat and sheep have 87–98% homology [9]. Therefore, the cross-reactivity of goat and buffalo IgE antibodies with cow's milk caseins limits the use of products based on them in patients with CMPA [10].

Currently, it is recommended to prescribe products based on deep hydrolysis of bovine protein (whey or casein) or amino acid formulas for children with CMPA, depending on the form and severity [11, 12].

MAIN DIFFERENCES BETWEEN GOAT'S AND COW'S MILK

1. Protein component of milk

Goat and cow's milk are casein-dominant products as the major proteins are represented by 80% casein (CN) and only 20% whey proteins (globulins — β-LG and albumin — α-LA).

Analysis of the composition of major nutritional milk samples conducted at National Milk Laboratories (Wolverhampton, UK, 2019) noted

that compared to cow's milk, GM has a lower concentration of total protein and casein in particular [13].

The casein fraction includes different types: αS1-CN, αS2-CN, αS3-CN (the αS3-CN fraction is less than 3%, so it is rarely mentioned in the literature), β-CN, κ-CN [7].

GM proteins are different from cow's milk proteins. The former is dominated by low molecular weight proteins (α-LA and β-CN), which facilitates their digestion by proteolytic enzymes, reduces sensitisation and allergic attitudes not only from the gastrointestinal tract (GIT), but also from the whole organism [7]. In addition, M.E. Pintado and F.X. Malcata (2000) found faster hydrolysis and digestion of β-lactoglobulin by GM [14] and S. Bevilacqua (2001) suggested that low αS1-CN content in GM contributes to more efficient digestion of β-lactoglobulin [15].

At the turn of the century, the properties of α-casein GM were actively studied. The hypothesis of genetic regulation of αS1-CN production has been proposed. At least 10 different genetic variants were found to affect the expression of αS1-CN phenotype, which are related to goat breed, milk composition and coagulation properties [16, 17]. Later, it was reported that in goats, about 16 alleles are associated with αS1-CN protein synthesis [18].

C. Cebo et al. (2012) in their work showed that genetic polymorphisms in the αS1-CN locus affect both the structure and composition of milk fat globules. It has even been observed that in mid-lactation, goats with the αS1-CN genotype produce larger fat globules with low levels of polar lipids in the milk fat globule membrane (MFGM) than goats with the αS1-CN null genotype [19].

Recently, the β-casein protein fraction has gained clinical importance. The gene responsible for β-CN production has two common alleles, A1 and A2, which are characterised by the presence of different amino acids at the 67th position. Thus, the A1 allele contains the amino acid histidine, while A2 contains proline. In the milk of goats and sheep, β-CN-A1 is practically absent and the milk of these animals is sometimes called A2 milk [20, 21].

Under the action of peptidases β-CN-A1 β-casomorphins are formed in the stomach from β-CN-A1: BCM-5, BCM-7, BCM-9, which can act as ligands to opioid receptors. In animal experiments it was shown that oral administration of β-casomorphins affects the motility of the digestive tract and exhibits analgesic effect [9, 22, 23]. It does not occur when β-CN-A2 is digested [21, 24].

BCM-7 has been found to slow intestinal motility, cause abdominal bloating, abdominal pain, and increase the synthesis of proinflammatory cytokines (myeloperoxidase and IL-4) and faecal calprotectin [20, 25, 26].

In a study by J.S.J. Chia et al. (2017) provided evidence that BCM-7, derived from β-CN-A1, serves as a trigger for the development of type 1 diabetes mellitus in people with hereditary predisposition [27]. In addition, BCM-7 is considered as a possible cause of the development of sudden death syndrome in children and the formation of neuropsychiatric disorders such as autism and schizophrenia [28].

The difference in the digestion of goat and cow milk proteins *in vitro* has been noted. Thus, 96% of goat casein is completely hydrolysed by trypsin and only 76–90% of cow casein [29]. The low content or complete absence of αS1-casein in GM, as shown above, with a relatively high albumin content, favours the formation of a soft, delicate clot and small loose flakes, facilitating the digestion of milk by proteolytic enzymes [15, 21, 26–31].

GM differs little from cow's milk in amino-acid composition. GM contains slightly more leucine, while cow's milk contains isoleucine. The amount of valine is similar in both types of milk. GM has a relatively lower content of the essential amino acid lysine, but a higher level of the essential amino acid histidine, which is essential for children, and the sulfur-containing amino acid cystine, which is able to bind heavy metals and is recognised as a powerful antioxidant [32].

It is especially necessary to note the high level of taurine in GM, which is 20–40 times higher than in cows' milk [33]. Taurine is involved in the formation of bile acid salts, osmoregulation, antioxidant defence, calcium transport, central nervous system activity, blood pressure regulation, reduces cardiovascular disorders [34], increases tolerance to physical activity, due to which it is often used in combination with steroids to improve metabolic processes [35].

Of particular importance are the growth factors contained in GM, which can stimulate cell growth and the expression of various functions. In studies on laboratory animals it was found that transforming growth factor β (TGF-β) reduces the severity of inflammatory reaction, induces the synthesis of secretory IgA in the intestine and participates in the formation of immunological tolerance [36,

37]. Insulin-like growth factor 1 (IGF-1) regulates the growth processes of bone and cartilage tissue, thus providing prevention of osteoporosis, and also stimulates gut maturation in rats [36, 38].

It should be noted that both cow's and GM have a complex plasmin enzyme system consisting of plasmin (PL), plasminogen (PG), plasminogen activators (PA), plasminogen activator inhibitors [39].

For the first time I. Politis et al. (1994) demonstrated that tissue plasminogen activators (t-PA) are located in casein and serum fractions of GM, and urokinase plasminogen activators (u-PA), in addition, in somatic cells [39].

Electrophoretic studies by A.J. Trujillo (1997) showed that plasmin hydrolyses the same regions of β-casein in bovine and GM [40]. The plasmin system is also involved in mammary involution. Moreover, higher PL and PA activity is observed in late lactation of cows [41].

The effect of casein fractions on the state of intestinal microbiota was evaluated by sequencing of *16SrRNA* gene in experimental animals. The study revealed correlation of β-casein with bacteria of *Enterococcus* and *Allobaculum* genera, and αS1-casein — with microorganisms of *Akkermansia*, *Bifidobacterium* and *Eubacterium* genera. It was observed that the formation of the intestinal microbiome was slightly more active when mice were fed with GM, and the metabolic rates of pyruvate, nucleotides and linoleic acid were significantly higher than with cow's milk [42].

In a recent study, the benefits of GM peptides were investigated and proved that they have the potential to inhibit IL-6 overexpression and control COVID-19 disease. In this study, peptides derived from β-lactoglobulin, which inactivates both the virus and its receptors in the host cell, were identified using *in silico* computer analysis. The following candidate peptides were studied: *YLGYLEQLLR*, *VLVLDTDYK* and *AMKPWIQPK* with strong conformations demonstrated the ability to bind to the IL-6 receptor, inhibiting the activity of SARS-CoV-2 virus without adversely affecting other proteins of the immune system [43].

2. Fat component of milk

Goat's milk fat resembles cow's milk fat in relation to the lipid fractions of whole milk and cream, containing 97 to 99% free lipids, of which 97% are in the form of triglycerides. Bound lipids (1–3%) are represented by neutral fat, glycolipids and phospholipids.

The main distinguishing criteria of GM fat composition are, firstly, the relatively small size of fat globules, which are about 10 times smaller than those of cow's milk, and, secondly, the fact that non-fat GM has more free lipids than cow's milk [7, 44].

GM lacks agglutinin, which 'glues' fat globules together. Therefore, the small globules create a larger surface area available for the action of pancreatic lipase, providing a relatively high digestibility of GM fat compared to cow's milk fat [44, 45].

In addition, a peculiarity of GM fat is its fatty acid composition: it has a significantly higher content of short- and medium-chain fatty acids (SCFAs and MFAs: caproic, caprylic, caprine, lauric and myristic acids [7]).

It is well known that SCFAs are an energetic substrate for enterocytes that repair damaged intestinal mucosal cells, which improves nutrient transport across the basolateral membrane [46].

MFAs are absorbed in the intestine directly into the venous network, bypassing the lymphatic network, without the involvement of pancreatic lipase and bile acids, which facilitates the digestion of goat fat, unlike cow fat [47].

SCFAs and MFAs have antibacterial and antiviral properties and dissolve cholesterol deposits.

In terms of unsaturated fatty acid content, GM is superior to cows' milk as it includes higher amounts of monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) with their derivatives such as eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), which have beneficial effects on all human tissues and organs [7, 13].

The lipoprotein lipase (LPL) system of GM is lower than that of cows. It is more tightly bound to fat globules (compared to casein micelles in cows) and has a pronounced correlation with spontaneous lipolysis (lipolysis at 4 °C). LPL activity in animals is affected by the stage of lactation, milking frequency, starvation and lipid supplementation [48].

3. Carbohydrate component of milk

The main carbohydrate in GM, as in any other milk, is lactose, the concentration of which is comparable in goat and cow's milk.

The second carbohydrate ingredient of GM is oligosaccharides, the level of which is 4–10 times higher and the "palette" of their structure is more diverse than in cow's milk [49–52]. In total, GM contains about 40 different oligosaccharides [52, 53].

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The profile of oligosaccharides, in contrast to cow's milk, is similar to breast milk oligosaccharides (BMOs). Therefore, they can be considered as a natural source of human oligosaccharides with positive effects on the health of GM receivers [54].

The functions of oligosaccharides are related to biological and antibacterial properties. Reaching the small intestine, oligosaccharides stimulate the growth of commensal microbiota, block pathogen receptors, inhibit the thermostable fraction of E. coli enterotoxin, and inhibit the interaction between leukocytes and endothelial cells, thus fulfilling an anti-inflammatory function [54].

The anti-inflammatory effect of oligosaccharides was demonstrated in experimental animal models with hapten-induced and dextran-sulfate-sodium induced colitis [55, 56].

4. Mineral substances and vitamins of milk

Minerals are essential to the human body as they play many vital functions including, but not limited to, activation of cofactors, enzymes, metalloproteins, bone formation, oxygen transport, and others.

Milk from goats and cows contains high congruent concentrations of calcium and phosphorus. At the same time, the GM content of iodine, potassium, copper, manganese, molybdenum is higher, and sodium, sulphur, zinc — lower than in cow's milk [57].

Some articles report lower iron values in GM [58, 59], which is attributed to genetic variability of dairy goat breeds, climatic and geographical zones of pasture location, and differences in feed composition. But, despite this, in some experimental studies the better bioavailability of iron and calcium from GM compared to cow's milk was noted [60, 61].

As in any milk, in the milk of the discussed farm animals determine almost identical content of some vitamins, namely: B_1, B_2, B_6, D [15, 57, 62]. However, there are also differences. Thus, in GM, compared to cows, the level of ascorbic acid and retinol is higher, while folate and vitamin B_{12}, necessary for normal hematopoiesis, are lower [61, 62].

Insufficient content in GM of a number of essential nutritional factors, vitamins and trace elements, in particular, vitamin B_{12}, folic acid and iron can lead to anaemia, accompanied by disorders in the development of the central nervous system and the formation of the immune response.

An illustration of the above is the work of C.A. Elvehjem (1953), which was carried out in the middle of the last century, but has not lost relevance and today. In his scientific work the author showed that when rats were fed GM they had a slower growth rate than when they were given cow's milk. The addition of folic acid and cyanocobalamin to the diet of laboratory animals helped to accelerate growth performance. Apart from experimental studies, clinical observations have recorded cases of severe anaemia in infants associated with receiving GM. In this regard, the term "goat milk anaemia" was even introduced [63].

Folic acid and vitamin B_{12} deficiency in children receiving GM exclusively was the subject of research in 1970 on megaloblastic anaemia and continues to be a concern today [64–66].

5. Cellular components of milk

It has long been known that goat milk naturally contains increased levels of somatic cells (SCC) and some isoflavonoids compared to cows due to the apocrine secretory system of the mammary gland [13, 67]. The special live SCC defence cells destroy pathogenic bacteria in the gut and stimulate the growth of beneficial microbiota. Phytoestrogens, including lignans, isoflavones, and coumestans (particularly equol), have been associated with the reduced risk of cardiovascular disease, type 2 diabetes mellitus, cancer, and symptoms of osteoporosis, metabolic syndrome, and menopause [13].

GOAT MILK-BASED FORMULAS

Although BF is the most appropriate way to feed infants in the first months of life, most infants stop receiving the mother's breast during this period of life [68–72].

According to the Federal State Statistics Service of Russia, as of December 2020, the number of children receiving mother's breast from 3 to 6 months of age was 43.9% and from 6 to 12 months — 39.2% [71]. At the same time, the average duration of only BF (when a child receives only the breast of his/her biological mother) corresponded to only one month against the WHO recommended 6 months, predominantly BF (along with breast milk, irregular supplementation with formula milk in the amount of no more than 100 ml per day or other liquid/thick food in the amount of no more than 30.0 ml per day is possible) — 4 months, and the total duration of BF (only BF + predominantly BF) — 10.6 months

[72]. Among all regions of the Russian Federation, Moscow has the lowest duration of BF: only BF — 0.3 months, predominantly BF — 2 months, any BF — up to 6 months on average. This low frequency of BF is most likely due to the intensity of life in the country's largest metropolitan area and the mother's earlier retirement from her maternity leave [73].

There are different reasons and circumstances in which a child is deprived of mother's milk. But whatever the case, it should always be remembered that the introduction of complementary feeding or complete transfer of the child to artificial feeding (AF) should be strictly justified and carried out only when the need to introduce milk formula into the child's diet is objective, and the entire arsenal of means aimed at stimulating lactation has proved ineffective.

In such a situation, the paediatrician is always faced with the difficult question of choosing a high-quality milk formula, which, although developed with maximum adaptation of farm animal milk to the composition of breast milk, can never be a complete copy of it.

The growth in global GM production has prompted the creation of milk formulas and the entire line of infant nutrition products based on it, since whole milk from ruminants, including goats, is not recommended for consumption by infants. This restriction is due to the mismatch of GM composition with female composition and the imperfection of the infant's gastrointestinal tract to digest and assimilate phylogenetically not provided food [74–76]. Scientists have proved that consumption of any kind of whole milk (goats, cows, sheeps, etc.) with high concentration of protein and mineral compounds by children of the first year of life disturbs the function of kidneys, liver, secretory activity of the digestive tract, irritates the intestinal mucosa with subsequent development of microdiapedesis haemorrhages, increases intestinal permeability for food proteins, causing sensitisation and azotemia [62, 74].

In connection with the foregoing, despite the good digestibility of GM milk protein, fat, microelements in adults, for the nutrition of infants, it is necessary to use infant formulas based on it, to the maximum extent adapted to the "gold standard": the composition of women's milk [74, 77].

Goat milk-based infant formulas (GMF), which are approved by the European Food Safety Authority (EFSA), are available in many countries of the world, including Russia [78].

A systematic review and meta-analysis of four randomised controlled trials (RCTs) conducted in accordance with the recommendations of the Cochrane Guidelines [79] summarised the current evidence on the effectiveness of goat milk-based starter formulas (GMF) compared with identical cow's milk-based formulas (CMF) and presented the results in accordance with the Reporting for Systematic Reviews and Meta-Analyses (PRISMA) [80]. Children on exclusively BF served as controls. The data presented showed no significant differences in anthropometric parameters and stool frequency, or in symptoms of food allergy and/or atopic dermatitis between children fed GMF compared to CMF. Adverse events were similar in both groups [81].

There is no doubt that GM has high nutritional value and beneficial properties [82, 83]. RCTs have proved the adequacy of using GMF in the nutrition of both healthy infants and infants with severe nutritional deficiencies in comparison with CMF. The dynamics of weight-growth gains on the background of receiving the investigated products in the groups were identical [84, 85].

To confirm the safety and biological value of GMF, it is necessary to assess the taste preferences of young patients, since the sensory characteristics of infant milk formulas are the key factor contributing to their acceptance by a child on formula feeding.

Most studies have investigated the palatability of conventional CMF compared to formulas based on soya or deep hydrolysis of BKM [86–89].

A multicentre, double-blind, multicentre RCT conducted in and around Paris evaluated the eating behaviour and appetite of children in the first four months of life on AF. A total of 64 healthy infants participated in the study and were divided into two groups based on the product offered (GMF and CMF). The authors noted that infants who received GMF showed better overall appetite than infants who were fed with CMF. This diversity in infants preference may have been due to differences in the composition of these formulas, namely protein and lipid profiles. In addition, babies fed GMF had a better quality of life. There was no difference in food enjoyment between the groups [90]. These results suggest that GMF may be an attractive alternative to CMF.

The composition of GMF is not significantly different from CMF, but there are some special characteristics that provide the former product with technological (physicochemical) advantages

[74, 77, 91, 92]. This is most likely due to the composition of the raw materials used for the production of these formulations. The composition of milk nutrients has been found to be influenced by several factors, the most significant of which are considered to be: type and age of animal, breed, method of animal husbandry, season of milk collection, milking method, diet and duration of lactation [93–95]. For example, H.C. Lythgoe directly analysed 335 samples from individual goats from 21 herds in Massachusetts back in 1940. Milk samples were collected over a period of 16 months. The work confirmed high individual and seasonal variability in total solids content. This was primarily related to variability in the fat component, which was more pronounced in goats than in cows [96].

Recently, much attention in the development of infant formulas has been paid to biologically active components such as free amino acids, nucleotides, polyamines, and growth factors because they are contained in breast milk [77].

The use of innovative technologies in the manufacture of adapted products for infants makes it possible to preserve all those valuable natural components present in whole GM and to balance its composition in accordance with regulatory documents [97, 98].

In the formulas, as in whole milk, α-lactalbumin and β-CN remain dominant, with β-CN-A2, and αS1-CN is practically absent, which resembles the protein composition of women's milk. Due to this combination of proteins, it is possible to reduce the symptoms of digestive discomfort (such as colic, bloating, abdominal pain, defecation difficulties) in infants [74, 77].

The fat component of the formula is enriched with essential PUFAs of the omega-3 and omega-6 class, and recently their derivatives: docosahexaenoic (DHA) and arachidonic (ARA) fatty acids have been introduced. This brings the composition of the product closer to the fatty acid spectrum of breast milk. The biological role of long-chain PUFAs is in the synthesis of eicosanoids (prostaglandins and leukotrienes) that regulate the processes of inflammation and immune response, as well as in the formation of virtually all cell membranes of the body, especially in nerve cells of the brain and eyes. DHA makes up about 40% of all polyunsaturated fats found in the human brain. Formulas manage to retain small-sized fat globules [74, 77].

The total lactose content of the formulas is close to the recommended content. Oligosaccharides are naturally present in infant GMFs. In a study by A. Leong et al. (2019) investigated the prebiotic and anti-infective properties of natural oligosaccharides in infant formulas (starter and follow-up) based on goat's milk. The results proved the bifidogenic (enhanced growth of bifidobacteria and lactobacilli) and antipathogenic adhesive properties (reduced adhesion of *E. coli NCTC 10418* and *S. typhimurium)* of the oligosaccharides present in the products. In addition, 14 oligosaccharides similar to those found in whole GM were identified in the formulas. Of these, five (2'-fucosyl-lactose, 3'-sialyl-lactose, 6'-sialyl-lactose, lacto-N-hexaose and lacto-N-neotetraose) were found to be identical to breast milk oligosaccharides (BMO). Of great importance, these 14 studied GMFs retained their properties during heat treatment during formula production [52–54].

Dairy GMFs contain vitamins and minerals according to the physiological needs of children.

Considering the low level of vitamins E, C, B_{12}, folic acid, iron in GM, these important nutrients are necessarily added to the composition of the products. In addition, they are introduced: L-carnitine, taurine, choline, nucleotides, which favourably affect metabolic processes in the body, brain and vision development, maturation of the immune and digestive systems [74, 77].

An extremely important aspect in the development of milk formulas is the osmolality index (the number of osmotically active particles in 1 litre of solution), which is determined by the concentration of proteins and salts. The permissible concentration is calculated in such a way that the kidney load is within the capacity of the infant's body. The osmolality of breast milk is 240–280 mOsm/l, which corresponds to the capabilities of the child's organism. It is no coincidence that these values serve as the "gold standard" and are recommended by WHO for starter milk formulas [97, 98].

CONCLUSION

Thus, milk formulas, especially starter formulas based on goat's milk, have a strictly balanced macro- and micronutrient composition, are enriched with essential nutritional factors, comply with sanitary and hygienic requirements for this category of food products to ensure optimal growth and development of infants, which allows us to consider them as an alternative to modern infant formulas based on cow's milk and to use them in the nutrition of not only healthy infants, but also in the presence of a mild form of malnutrition.

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DENSITOMETRY IN THE ASSESSMENT OF BONE METABOLISM IN CHILDREN WITH CELIAC DISEASE

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Abstract. The active growth and development of a child may be accompanied by disorders of bone metabolism, and if the child has a chronic pathology of the gastrointestinal tract, then the risk of a decrease in bone mineral density increases manifold. Gluten intolerance is often accompanied by disturbances in nutritional status, in particular changes in bone tissue. An important aspect of dynamic monitoring of patients with celiac disease is monitoring the state of bone mineral density in order to timely detect and correct changes that have occurred. Densitometry today is not a routine diagnostic method and is not included in research protocols for gluten intolerance; however, literature data confirm the relevance of using this technique both among adults and in the pediatric population. The article presents studies that show the presence of a decrease in bone mineral density both at diagnosis of celiac disease and during subsequent follow-up. Arguments in favor of densitometry are presented and risk factors for decreased bone turnover are identified. An integrated approach to assessing the effectiveness of diet therapy and the nutritional status of patients, if followed, will significantly improve the quality of life of children.

Keywords*: bone metabolism, bone mineral density, celiac disease*

ДЕНСИТОМЕТРИЯ В ОЦЕНКЕ КОСТНОГО МЕТАБОЛИЗМА У ДЕТЕЙ С ЦЕЛИАКИЕЙ

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Резюме. Активный рост и развитие ребенка может сопровождаться нарушениями костного метаболизма, а если ребенок имеет хроническую патологию желудочно-кишечного тракта, то риск снижения минеральной плотности костной ткани кратно возрастает. Непереносимость глютена зачастую сопровождается нарушениями нутритивного статуса, в частности, изменениями со стороны костной ткани. Важным аспектом динамического наблюдения за пациентами с целиакией является контроль за состоянием минеральной плотности костной ткани с целью своевременного выявления и коррекции возникших изменений. Проведение денситометрии в настоящее время не является рутинным методом диагностики и не включено в протоколы исследования при непереносимости глютена. Однако литературные данные подтверждают актуальность использования данной методики среди взрослых и в детской популяции. В статье приведены исследования, которые показывают наличие снижения минеральной плотности костной ткани как при постановке диагноза «целиакия», так и при последующем наблюдении. Приводятся аргументы в пользу проведения денситометрии и указываются факторы риска снижения костного метаболизма. Комплексный подход к оценке эффективности диетотерапии и нутритивного статуса пациентов при ее соблюдении позволит в значительной степени улучшить качество жизни детей.

Ключевые слова: *костный метаболизм, минеральная плотность костной ткани, целиакия*

In recent years, the concept of gluten intolerance has changed dramatically, and the pathology has evolved from a gastroenterological nosology into a multiorgan disorder that requires a comprehensive approach in the assessment of clinical manifestations, diagnosis, and careful evaluation of the dynamics of the clinical picture in further therapeutic support after the prescription of a gluten-free diet (GFD) [1–3]. The widespread and multifaceted clinical picture of gluten intolerance suggests that a physician of any speciality may encounter this pathology or its complications [4–6].

Changes in bone metabolism can be both a complication due to malabsorption syndrome in gluten intolerance and the only manifestation of the disease [7, 8]. Assessment of nutritional status parameters and, in particular, bone metabolism, is an integral part of the therapeutic management of paediatric patients with chronic diseases, especially of the gastrointestinal tract [9–13]. Several studies confirm that changes in bone mineral density (BMD) are observed in patients of all ages at the time of diagnosis of gluten intolerance [14, 15]. For adult patients, ACG and ESsCD guidelines have been developed, which include performing densitometry in patients over 40 years of age or in the presence of symptoms of malabsorption at the time of diagnosis of celiac disease [16, 17]. The study by F. Tovoli et al. (2023), in which they evaluated the dynamics of bone metabolism in patients with low densitometry values at diagnosis and after the use of nutritional therapy for 10 years, shows that BMD values stabilise with long-term dietary restriction of gluten [15]. We obtained similar results earlier in paediatric practice. During the examination of 32 children who had been following the GFD for more than 6 months since the diagnosis of celiac disease, a decrease in BMD at densitometry of the lumbar spine was found in 18.75% of children, half of whom had low values. A significant dependence of bone mineralisation reduction on the quality of dietary adherence was revealed: the more often the child violated the diet, the lower the BMD. There was no history of fractures in the patients [7].

During analysis of literature data published between 1996 and 2017, BMD levels were found to be lower in children with celiac disease compared to healthy peers [18]. In this regard, it is worth noting the important aspect of dynamic monitoring of BMD status during adherence to dietary therapy, especially when patient adherence is low. In this case, the frequency of densitometry should be approached individually, depending not only on adherence to diet therapy, but also on the patient's age, nutritional status, in particular, physical development and quality of symptom control.

However, contrary data exist. When densitometry was performed in 24 children with celiac disease (12 boys aged 8.7±3.3 years) at diagnosis and after the use of GFD in therapy and subsequent comparison at two stages of the study in each patient, it was found that BMD within reference values was noted in all patients studied at the time of diagnosis and after treatment, with no difference between the two points of analysis [19]. A retrospective study including 86 patients with celiac disease aged 2–18 years evaluated the relationship between the z-scores of lumbar BMD calculated according to their chronological age and height and their clinical, laboratory and histopathological parameters. The authors found that BMD according to densitometry data when assessed according to chronological age ≤-2 standard deviation (SD) in 26.7% of patients, and when assessed according to height, the number of patients with ≤–2 SD decreased to 12.8% of patients and correlated with their age at the time of celiac disease diagnosis (r value=0.269). At the same time, no statistically significant differences between subgroups, between BMD values with respect to their clinical, laboratory and histopathological parameters were found in any group [20].

However, differences in BMD in patients with celiac disease are more frequently noted. In a cohort retrospective study, we analysed demographic, clinical and laboratory data from the medical records of: 673 children with celiac disease (63% female, mean age at diagnosis 10.6 years, interquartile range 7.8–13.9) who underwent densitometry at diagnosis. Logistic regression analysis showed that the mean aBMD-Z score at the initial scan of the children at the time of diagnosis was –0.4±1.2. Forty-six children had aBMD-Z scores less than -2 (6.8%; 95% 5.2–9.0). Those who underwent BMD reanalysis (n=108; 16.0%) had a significant increase in aBMD-Z score (mean change 0.29; p=0.0005). A higher body mass index (BMI) was associated with a more insignificant likelihood of a low aBMD-Z score at initial densitometry (0.46; 95% 0.35–0.50). BMI-Z scores greater than –0.4 identified children with low aBMD-Z at their initial BMD analysis (p=0.05). According to the authors, BMI-Z scores can be used to identify children with

celiac disease at risk of low BMD who should undergo densitometric screening [21].

A cross-sectional study conducted in Iran (2023) included 48 children (mean age 9.96±3.17 years) diagnosed with celiac disease (Marsh II and Marsh III stages). The authors proved that 35.4% of the patients had BMD within the normal range, 41.7% had values at the lower limit, and 22.9% had low bone mineralisation in femoral bone examination by densitometry. When lumbar densitometry results were evaluated, it was found that 39.6% had BMD within reference values, 25% had BMD at the lower limit of normal, and 35.4% were diagnosed with low BMD. No statistically significant correlation was between age, sex, place of residence, Marsh stage, adherence to GFD and bone densitometry in both areas. A statistically significant correlation was found between BMD in the lumbar region and two HLA types, namely HLA DQ8 and HLA DQ2/8 (p=0.016). Thus, the authors confirm the frequent occurrence of low BMD in children with first diagnosed celiac disease [22].

In a study involving children with celiac disease detected by screening and patients without celiac disease, BMD was assessed by densitometry, serum 25 (OH) vitamin D3, parathyroid hormone (PTH), interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-15, gamma interferon and tumour necrosis factor alpha. It was found that at the time of diagnosis, children with celiac disease detected at screening had an average –0.03 g/cm lower BMD of both whole body and spine compared to controls (p=0.009 and p=0.005 respectively), also an average –11.4 nmol/l lower 25(OH) vitamin D3 level (p <0.001) and an average +1.0 pmol/l higher PTH level (p<0.001). Systemic levels of cytokines IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-13 and tumour necrosis factor alpha were elevated in celiac disease detected at screening compared to controls (p<0.001). No differences in IPC, 25(OH) vitamin D3, PTH and cytokine levels were found in children receiving GFD compared to controls [23]. This study confirms the diagnostic significance of BMD control in patients with celiac disease. Due to the fact that patients with celiac disease are often diagnosed with reduced blood vitamin D levels, it is considered appropriate to perform dynamic BMD monitoring using densitometry [24].

BMD assessment is an important component of a comprehensive assessment of children's health; timely diagnosis of decreased bone metabolism will reduce the number of patient hospitalisations and the number of visits to specialists, preserving the quality of life of children and their families [25–27].

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

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PATHOGENETIC MECHANISMS OF DEVELOPMENT OF BONE TISSUE PATHOLOGY IN CHRONIC GASTROINTESTINAL DISEASES

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Abstract. The review describes the symptoms of damage to the skeletal system in celiac disease, chronic gastritis, the condition after gastrectomy and inflammatory bowel diseases. The state of the vitamin D system and bone metabolism in chronic diseases of the digestive system, the mechanisms of the influence of vitamin D on the state of the intestinal mucosa, and risk factors contributing to pathological changes in bones in gastrointestinal diseases are presented. The review shows that in most cases, impaired bone mineral density in diseases of the digestive system is caused by impaired phosphorus-calcium metabolism, metabolism of the vitamin D system and impaired intestinal microbiocenosis, and specific mechanisms for each nosological form require further study.

Keywords: *bone metabolism, vitamin D, calcium, bone mineral density, intestinal microbiocenosis*

ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ РАЗВИТИЯ ПАТОЛОГИИ КОСТНОЙ ТКАНИ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Резюме. В обзоре описаны симптомы поражения костной системы при целиакии, хроническом гастрите, после резекции желудка и при воспалительных заболеваниях кишечника. Описаны система витамина D и костный метаболизм при хронических заболеваниях органов пищеварения, механизмы влияния витамина D на слизистую оболочку (СО) кишечника, факторы риска, способствующие патологическим изменениям костей при заболеваниях ЖКТ. В обзоре показано, что в большинстве случаев нарушение минеральной плотности костей при заболеваниях органов пищеварения обусловлены нарушением фосфорно-кальциевого обмена, обмена системы витамина D и нарушением кишечного микробиоценоза. Причем конкретные механизмы при каждой нозологической форме требуют дальнейшего изучения.

Ключевые слова: *костный метаболизм, витамин D, кальций, минеральная плотность костей, микробиоценоз кишечника*

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The course of any chronic disease negatively affects the processes of bone modelling and remodelling. The bone tissue loses its metabolic rate, especially in childhood. As a result, bone mass does not reach proper values, which creates the ground for the formation of low bone mineral density (LBMD) and osteoporosis in the future [1].

Researchers in recent decades have identified characteristic changes that have occurred in the course of chronic digestive diseases in children. They include early debut, frequent relapses, and an increase in combined gastrointestinal pathology. In this case, the process of inflammation in the mucosa of the stomach and small intestine has widespread and pronounced morphological changes, up to atrophic [2]. Disruption of nutrient breakdown and absorption processes in chronic gastrointestinal diseases with malabsorption syndrome in children is often combined with low disharmonious indicators of linear body size and changes in bone remodelling [3]. Prolonged micronutrient deficiency, including vitamin D deficiency in children with gastrointestinal pathology can lead to reduction in bone mineral density [3–7].

Literature data clearly indicate that the role of the upper digestive system (stomach and duodenum) in the absorption of micronutrients, especially phosphorus, calcium and vitamin D, is of paramount importance [7]. Vitamin D affects bone mineral density by regulating calcium absorption in the gastrointestinal tract and influencing the RANK/RANKL/OPG system [8]. Phosphorus, calcium and vitamin D deficiency in gastrointestinal pathology leads to symptoms of osteomalacia: frequent fractures, bone pain in various localisations, posture disorders in sagittal and frontal planes, and limb deformities [1, 3, 9]. Such symptoms have been described in the case of celiac disease, chronic gastritis, condition after gastric resection and inflammatory bowel diseases.

$1,25(OH)_2D$ have also been shown to be involved in immune cell differentiation, modulation of the gut microbiota, gene transcription and barrier integrity, maintenance of the integrity of mucosal tight junctions, improvement of folic acid absorption and activation of cytochrome P450 3A4 expression [10].

The following mechanisms of vitamin D effect on the intestinal mucosa (IM) have been described: regulation of colonic IM mucus secretion [11], ensuring structural integrity [12], influence on the composition and functions of the gut microbiota [13], increased expression of tight junction proteins, and suppression of zonulin release [14]. The effects of the vitamin D on the innate immunity system are associated with stimulation of production by neutrophils, macrophages and cells lining epithelial surfaces of antibacterial peptides with broad antimicrobial activity, such as cathelicidin (cAMP) and β-defensin 2 (DEFB4) [15–17], with increased antimicrobial action against some pathogens, induction of intracellular pathogen recognition receptor NOD2, improved transcription of cAMP and DEFB4, suppression of hepcidin antimicrobial peptide expression, and decreased ferroportin-mediated export of intracellular iron [18, 19]. The effect of vitamin D on adaptive immunity is to control the differentiation and maturation of dendritic cells, expression on monocytes of molecules involved in antigen capture, decrease the pro-inflammatory Th1 response, increase the anti-inflammatory Th2 response, increase the number of T regulatory cells, and limit the number of CD4+ T cells [20]. Due to these pleiotropic effects, vitamin D is associated with the activity of immune-mediated diseases — those forms of pathology in which lesions of both the bone system and the digestive tract are manifestations of autoimmune processes (inflammatory bowel disease, celiac disease, autoimmune gastritis) [21–23].

Different forms of vitamin D are in the bloodstream in the bound form with the VDBP receptor. And the active form of vitamin D ($1,25(OH)_2D_3$) due to binding to the receptor exerts various biological effects by interacting with the nuclei of target cells located in various organs and tissues, such as the immune system, pancreas, cardiovascular and muscular systems, and brain [24, 25].

The VDR gene is located on the short arm of chromosome 12 and contains 8 protein-coding exons (exons 2–9) and 6 untranslated exons (exons 1a-1f) [26, 27]. A large number of polymorphisms of the VDR gene have been described, which may affect VDR expression and function and subsequent vitamin D-mediated effects [28]. VDR also regulates the cell cycle, influences cell differentiation and proliferation, controls the development of cancer pathology, as well as inhibition of dendritic cell differentiation, and stimulation of the synthesis of a number of hormones [26, 29].

The effect of calcium on the gastrointestinal tract has been studied in basic research. It is known that calcium is a secondary messenger of cell metabolism regulation and a regulator of synaptic transmission. Its action on the gastric

and intestinal mucosa is regarded as astringent. It attenuates peristalsis by acting on smooth muscle. In foci of an inflammation, calcium stimulates reparative regeneration in the intestine and suppresses excessive proliferation of gastric cells. Calcium chloride thickens tissue and reducing the permeability of cell membranes [30].

Reduced absorption of Ca from the intestine due to accelerated chyme passage and reduced secretion of hydrochloric acid, which converts poorly soluble Ca compounds into soluble, well-absorbed calcium chloride, also plays a role in the genesis of osteopathies in gastrointestinal diseases [31–33]. It is possible to explain degenerative-dystrophic changes of the spine in children with digestive diseases from the point of view of innervation disorders in neurometamers. According to this concept, neurotrophic changes are primary. The pathology of the digestive and bone systems in adolescents and adults is secondary [34]. But there is another view — a recognition of the influence of irritation from the affected organ on the state of the musculoskeletal system, leading to muscle spasm, impaired mobility of motor segments in children, adolescents and adults, persons suffering from gastric and duodenal ulcer disease [35]. Cases of spasm of long back muscles leading to scoliosis in liver and gallbladder diseases have been described [35, 36]. Another possible cause of osteopathies in patients with gastrointestinal diseases is the use of medications that negatively affect bone tissue. These include glucocorticosteroids, anticonvulsants, thyroid hormones, anticoagulants and antacids, diuretics and nonsteroidal anti-inflammatory drugs, and some other drugs [37–41]. The results obtained in a number of studies indicate that long-term use of proton pump inhibitors (PPIs) increases the risk of osteoporosis-related fractures due to impaired Ca absorption and inhibition of osteoclastogenesis [40]. Moreover, the side effect of PPIs, in addition to suppression of the acid-forming function of the stomach, may be of a completely different nature. Undoubtedly, the pharmacological target of PPIs is H^+K^+-ATPase of parietal cells, which is an organ-specific enzyme [42]. But M. uzuki et al. suggested that PPIs can inhibit the activity of vacuolar H^+-ATPase enzyme, which is close in biochemical structure and is localised in the cytoplasm of many cells of the human body [43]. As a consequence, essential functions may be affected, including bone resorption, which is a necessary process for the restoration of normal bone. Recent studies have shown that long-term (for several years) use of PPIs for the treatment of chronic gastroduodenal pathology increases the risk of bone fractures as a manifestation of osteoporosis [40, 44, 45]. At the same time, hypocalcaemia and hypophosphataemia cause gastroduodenostasis and pathological gastroesophageal and duodenogastric refluxes due to the development of muscular hypotonia and impaired motor function of the stomach and gut [46].

Thus, pathogenetic mechanisms of the bone tissue pathology development in chronic gastrointestinal diseases in most cases are caused by disorders of phosphorus-calcium metabolism and vitamin D metabolism. Moreover, specific mechanisms in each nosological form require further study .

ADDITIONAL INFORMATION

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ROLE OF INTESTINAL MICROBIOTA IN THE GENESIS OF EPILEPSY

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Abstract. It is generally recognized that the health and well-being of a macroorganism depends on the adequate functioning of the gut microbiota and brain. It is noted that the gut microbiota is involved in the formation of brain functions through various pathways and systems, including the CNS. In such a situation, it is legitimate to assume that the microbiota may be a trigger in the development of epilepsy. Statistically significant differences in the microbial composition of feces between patients with epilepsy and healthy people were revealed. Epilepsy is a chronic brain disease of various etiologies. Moreover, in 40–60% of patients, the cause of this ailment remains unknown. Diversification of the gut microbial landscape has been shown to be accompanied by activation of epileptic paroxysms. However, the composition and structure of the intestinal microcosm is so complex and insufficiently studied that it is almost impossible to single out certain bacteria as the most "useful" or "dangerous" in epilepsy. It is assumed that excessive local synchronization of the bielectric activity of the brain is due to minimal chronic inflammation and leaky bowel syndrome with an imbalance in signal transmission along the brain-intestine axis. The main method of treating epileptic paroxysms is the prescription of pharmaceuticals. At the same time, in every third patient with epilepsy, refractory epilepsy occurs. The study of the species diversity, composition and function of the intestinal microbiota in patients with epilepsy, but with somewhat contradictory results, indicate the presence of intestinal dysbiosis in them and their potential value in the diagnosis and control of epilepsy treatment, especially in its refractory form.

Key words: *microbiota, epilepsy, paroxysm, nervous system, intestinal metabolites, neurotransmitter, short-chain fatty acids, ketogenic diet, probiotic, antibiotic*

РОЛЬ КИШЕЧНОЙ МИКРОБИОТЫ В ГЕНЕЗЕ ЭПИЛЕПСИИ

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Резюме. Общепризнанно, что здоровье и благополучие макроорганизма зависят от адекватного функционирования кишечной микробиоты и мозга. Отмечено, что кишечная микробиота принимает участие в формировании функций головного мозга через различные пути и системы, включая центральную нервную систему. В такой ситуации правомочно предположить, что микробиота может быть триггером в развитии эпилепсии. Выявлены статистически значимые различия в микробном составе фекалий между больными эпилепсией и здоровыми людьми. Эпилепсия — хроническое заболевание головного мозга различной этиологии, причем у 40–60% больных причина данного недуга остается неизвестна. Показано, что диверсификация микробного пейзажа кишечника сопровождается активацией эпилептических пароксизмов. Однако состав и структура кишечного микромира настолько сложны и недостаточно изучены, что выделить определенные бактерии как наиболее «полезные» или «опасные» при эпилепсии практически невозможно. Предполагается, что чрезмерная локальная синхронизация биэлектрической активности мозга обусловлена минимальным хроническим воспалением и синдромом «дырявого кишечника» с разбалансировкой передачи сигналов по

оси мозг–кишка. Основной метод лечения эпилептических пароксизмов — назначение фармацевтических препаратов. При этом у каждого третьего пациента с эпилепсией имеет место рефрактерная эпилепсия. Изучение видового разнообразия, состава и функции кишечной микробиоты у пациентов с эпилепсией, но с несколько противоречивыми результатами, указывают на наличие у них кишечного дисбиоза и на их потенциальную ценность в диагностике и контроле лечения эпилепсии, особенно при ее рефрактерной форме.

Ключевые слова: *микробиота, эпилепсия, пароксизм, нервная система, кишечные метаболиты, нейротрансмиттер, короткоцепочечные жирные кислоты, кетогенная диета, пробиотик, антибиотик*

INTRODUCTION

The gut microbiome (GMB) is a group of microorganisms that includes many prokaryotes (bacteria), eukaryotic microorganisms (such as fungi and protozoa), archaea and viruses that associate with the macroorganism [1–3].

In the modern world, the relationship of the macroorganism with gut microbes is the result of evolution over thousands of generations. Over millions of years, evolution has acted not only on our 23,000 genes, but also on nearly 4 million genes (both human and microbial) that are present in and on our bodies [4]. Metagenomic analyses have allowed the identification of seven dominant types of bacteria that contaminate the human gastrointestinal (GI) tract: *Firmicutes*, *Bacteroidetes*, *Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia* and *Cyanobacteria,* among which *Bacteroidetes* and *Firmicutes* account for more than 90% [5–7].

The study of the ontogenesis of the child's nervous system confirms the parallel development of the gut microbiome, the immune response and the central nervous system (CNS). The cognitive function of a child at the age of 2 years has been shown to be highly dependent on the qualitative composition of his or her gut microbiota in the first year of life [8].

In infancy, the brain has enormous metabolic capacity and activity. Comprising 5–10% of total body weight, the brain is responsible for almost 50% of the body's basal metabolic energy and is therefore particularly sensitive to reduced energy intake [9]. Due to the ability of microbial communities to control the amount of energy input, they can control the development of the nervous system during the first years of an infant's life.

Thus, the parallel maturation of the microbiome and CNS during the first stages of life suggests that the physiological development of the child's nervous system is possible if microbiome processes are optimised [10].

MICROBIOTA–GUT–BRAIN AXIS

OIt is generally recognised that the health and well-being of the macroorganism depend on the optimal functioning of the GMB and the brain. A number of experimental and clinical studies have shown that any negative impact on either the microbiota or the brain simultaneously results in damage to the functions of the two systems: the GI tract and the CNS. In other words, there is a bidirectional co-operation of the GMB with the brain, the so-called brain-gut-microbiota (BGM) axis [11–14], which is confirmed by the latest research on the microcosm of *Homo sapiens*.

It has been shown that changes in the structure of the gut microbiota lead to the development of not only intestinal diseases, metabolic disorders, allergic and autoimmune pathology, but also a number of neurological disorders, including neurodegenerative diseases (such as Parkinson's disease, Alzheimer's disease, multiple sclerosis), autism, depression, schizophrenia, and epilepsy. It has been observed that patients with epilepsy have a high incidence of digestive symptoms, and patients with inflammatory bowel disease (IBD) have a high predisposition to epilepsy [15–17]. In addition, statistically significant differences in faecal microbial composition have been found between epilepsy patients and healthy controls, as well as between patients with all forms of epilepsy before and after inclusion of ketogenic diet therapy [18–24].

Much of our understanding of interactions along the BGM axis is based on metagenomics and metabolomics data from experimental studies [25].

The complex bidirectional communications that link GMB to the brain encompass mitochondrial function, axis, hypothalamic-pituitary-adrenal, and autonomic, neurohumoral, enteroendocrine and immunomodulatory pathways. For example, it has been noted that GMB is able to modulate the enteric nervous system (ENS) and neuronal network through activation of the vagus nerve, immune and APUD system cells [8], as well as due to the synthesis and perception of pro- and anti-inflammatory cytokines, neurotransmitters (serotonin and GABA) and products of microbial metabolism such as secondary bile acids and short-chain fatty acids (SCFAs) [26]. The whole arsenal presented affects neuronal messages

and appears to regulate brain functions and therefore determines cognitive performance, behaviour, mood, presence of anxiety and/or depression [25, 27–29].

Experimental work performed on mouse models demonstrates the relationship of the gut microbiome with the levels of key neurotransmitters and single neuroreceptors in the brain. Gnotobionts (GF) show a drop in brain-derived neurotrophic factor (BDNF) expression, predominantly in the hippocampus [30]. Conversely, rodent models with a healthy microbiota show increased expression of BDNF, which is important for mediating neural stem cell proliferation [31]. Feeding GF mice with the probiotic *Lactobacillus rhamnosus* (JB-1) regionally and differentially modifies GABA receptor expression in them: there is an increase in expression in cortical regions and a decrease in prefrontal cortex and amygdala. These transformations in the expression of central GABA receptors are accompanied by changes in behaviour associated with anxiety and depression [25].

Other experimental studies have revealed a connection between GMB and the expression of N-methyl-D-aspartate (NMDA) [30], serotonin 1A [25] and tryptophan [13] receptors. The first receptor mediates the effects of the excitatory neurotransmitter glutamate [31], while the second and third mediate the effects of the inhibitory GABA.

In recent years, an aberrant microbiota profile has been shown to be associated with autism spectrum disorders, chronic pain, mood defects and affect development, and neurodegenerative diseases [12, 31–36]. This is clearly supported by scientific research. For example, transplantation of faecal microbiota (TFM) into GF mice from patients with Parkinson's disease caused motor deficits and neuroinflammation in rodents — two major features of Parkinson's disease [37]. In the GMB structure of patients with Alzheimer's disease compared to healthy individuals, a decrease in the level of microorganisms of *Firmicutes* phyla and *Bifidobacterium* genus and proliferative growth of *Bacteroidetes* phyla were observed [38]. In the faeces of patients with multiple sclerosis, researchers found high levels of *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* [39].

Considering that the gut microbiota is involved in the formation of brain function through various pathways and systems, including the CNS, it is reasonable to assume that it may also be involved in the development of the epilepsy [40].

GUT MICROBIOM AND EPILEPSY

Epilepsy is a chronic polyetiological brain disease characterised by recurrent unprovoked (or reflex) seizures of motor, autonomic, sensory and mental disorders resulting from excessive neuronal discharges [41–43].

According to data published in the Lancet (2019), epilepsy affects more than 70 million people around the world [44]. The debut of the disease is mainly occurr in childhood (about 75% of all episodes) [45]. The mechanisms of paroxysms are quite complex and the etiological factors are multifaceted. Although still in 40–60% of patients the cause of epilepsy remains unknown [41, 46, 47]. Is it correct to identify any seizures with epilepsy in such a situation? Certainly not, since situationally determined seizures "theoretically" have significant differences from epileptic seizures.

Firstly, epileptic paroxysms in most cases have a recurrent, predominantly stereotyped character. Moreover, their recurrence occurs without provocation by external and internal stimuli. However, as always, there are exceptions to the rule, and in some forms of the disease there is polymorphism of seizures.

Secondly, in epileptic recurrent seizures, nerve cell death occurs in the brain, whereas in situational seizures there is more often brain oedema without neuronal death.

Thirdly, it is the presence on the electroencephalogram of specific changes in epilepsy. Although, if the patient has rare paroxysms, electrical markers of diagnosis may be absent. And epileptiform discharges on the EEG can occur in patients without seizures.

However, in clinical practice, diagnosis of epilepsy is often a difficult problem that must be solved because patients with epilepsy have an increased risk of mental illness, which increases their disability and mortality. And the presence of uncontrolled paroxysms can lead to impaired memory, cognitive function and intelligence, delayed psychomotor development and even brain death.

The most popular way to treat epileptic paroxysms is to prescribe pharmaceutical drugs. However, one in three patients with epilepsy cannot be treated with anticonvulsant therapy, i.e. they have refractory (resistant) epilepsy [48]. The International Antiepileptic League (ILAE) task force defined drug resistance as "the failure of adequate trials of two tolerated, appropriately selected and used antiepileptic drug regimens (whether as monotherapy or in combination) to achieve sustained seizure-free epilepsy" [49].

Alternative therapies: ketogenic diet (KD), neurostimulation and surgery, which are resorted to in resistant epilepsy, do not always achieve a positive outcome. In order to justify the inclusion of new, more promising treatment regimens in epilepsy

management protocols, it is necessary to carefully consider the various etiopathogenetic mechanisms that may trigger the development of this disorder. Currently, scientists consider the gut microbiota as a possible trigger factor in the genesis of epilepsy [40].

The relationship of distortion of GMB composition has been established in models of epilepsy and in clinical studies. Rats with colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) have been shown to have increased susceptibility to pentylenetetrazole(PTZ)-induced epilepsy [50]. In a mouse model of PTZ-induced seizures, intestinal inflammation increases seizure activity and reduces the efficacy of antiepileptic drugs (AED). In turn, alleviation of inflammation induces specific antiepileptic effects [14]. Thus, a reversible inflammatory response was observed in the hippocampus of rats treated with TNBS, characterised by microglia activation and an increase in tumour necrosis factor alpha (TNFα). This suggests that gut inflammation increases CNS excitability and inversion of inflammation [50].

There is evidence that stress is able to rearrange the microbiocenosis. Simulated stress in rats provokes epileptic seizures and causes transformation of the gut microbiota [51, 52]. Transplantation of faecal contents of stressed rats to non-stressed animals generated in the latter an increased frequency and duration of seizures after basolateral amygdala excitation. At the same time, the inoculation of gut microbiota into mice with simulated stress from subjects not experiencing the disease prevented the convulsive effects of chronic stress in the former [52].

A recent study in mice found that intestinal inflammation increases pharmacologically induced seizure readiness [17], and administration of anti-inflammatory drugs reduced susceptibility to paroxysms and restored the efficacy of antiepileptic drugs.

In WAG/Rij rats of a genetic model of absent epilepsy at one month of age and before the onset of paroxysms, a change in GMB with a lower *Bacteroidetes/Firmicutes* ratio was detected. In 4 months after the debut of absences, an inverse correlation was recorded: an increase in the frequency of seizures was accompanied by a further decrease in the *Bacteroidetes/Firmicutes* ratio towards an increase in *Firmicutes* phyla microorganisms [22].

In another experiment, it was observed that gut microbiota infection triggered by Gram-negative bacteria, such as *Bacteroides fragilisor* representative of the normal colon microbiota of humans, can lead to the formation of cerebral cavernous malformations (CCM), structural abnormalities in brain capillaries that contribute to stroke and seizures in genetically predisposed mice [53]. Gnotobiont mice do not develop such cerebral abnormalities.

Analysis of the faecal microbiota by 16S ribosomal DNA sequencing in patients with pharmacoresistant epilepsy (PRE) and healthy individuals, including children aged 1 to 4 years, identified qualitative and quantitative abnormalities in GMB composition in the former relative to the latter. Patients with PRE had a decrease in the species diversity of gut microbiota with a predominance of *Firmicutes* phyla microorganisms, while in healthy individuals *Bacteroidetes* phyla were dominant [54].

In the work A. Peng (2018) it is noted that the number of microorganisms of the *Bacteroidetes* phyla and *Actinobacteria* class is suppressed in patients with the PRE compared to healthy controls, while the number of representatives of the *Firmicutes* phyla increases [8, 54]. The authors also revealed the dissimilarity of intestinal microcosm patterns in patients with the PRE and drug-responsive form of epilepsy. In the first group (n=49) compared to the second group (n=42), there was an increase in α-diversity, i.e., the diversity in the number of microorganisms within the family, abundance of rare bacteria, mainly belonging to the phylum *Firmicutes*. The microbial profile at the phylum level of patients with drug-sensitive epilepsy resembled that of healthy individuals: microorganisms of the phylum *Bacteroidetes* were dominant. In addition, an inverse correlation between the titre of bifidobacteria and lactobacilli in faecal samples and the frequency of seizures in patients was established, i.e. intensive growth of commensal microorganisms was accompanied by a reduction in the number of seizures [8].

Another picture of the microbial landscape described in the study of X. Gong (2020). In patients with PRE compared to healthy controls, there was a decrease in *Bacteroidetes* and *Proteobacteria* phyla, as well as enrichment of bacterial taxa of *Actinobacteria* and *Verrucomicrobia* phyla and other bacteria at the level of genus and family *Nitrospirae* and at the level of genera *Blautia*, *Bifidobacterium, Subdoligranulum, Dialister* and *Anaerostipes* ($p < 0.05$). Which means that specific strains of intestinal commensals are transformed according to clinical phenotypes, which may serve as a potential biomarker for disease diagnosis [18].

B. Şafak et al. (2020) performed a contrast analysis of the faecal microbiome between patients with idiopathic focal epilepsy (n=30) and a group of healthy individuals (n=10) and found that *Proteobacteria* and *Fusobacteria*, which can cause autoimmune diseases, were present in significantly higher titre in the first group compared to the

second. Bacteroidetes and *Actinobacteria*, which have positive effects on the immune system, were present in lower titre in the first group [19]. This work confirms the role of autoimmune mechanisms and inflammation in the etiology of epilepsy.

In a study led by K. Lee (2020), 17 species of bacteria were identified in the group of patients with epilepsy, while in the group of healthy people 18 species were identified [20]. E*nterococcus faecium, Bifidobacterium longum,* and *Eggerthella lenta* were found to be the strongest potential biomarkers in a group of patients with untreatable epilepsy [20].

The study of the α- and β-diversity in adult patients in both the PRE (n=23) and drug-responsive epilepsy (DRE) groups (n=21) showed no significant differences. Some differences in the composition of the gut microbiota were associated with the patients' response to AED. Thus, *Bacteroides Finegoldii* and *Ruminococcus* were significantly more frequently recorded in the DRE group compared to the PRE. Besides, the dissimilarity of representatives of the microcosm took place depending on the data of instrumental diagnostic methods. In individuals with normal magnetic resonance imaging (MRI) pattern *B. finegoldii* dominated, and in patients with normal EEG pattern — *Bifidobacterium* dominated [21].

Thus, studies of GMB species diversity, composition and function in patients with epilepsy, but with somewhat contradictory results, indicate the presence of intestinal dysbiosis and their potential value in the diagnosis and management of epilepsy, especially in its refractory form. However, the presented reorganisation of GMB in patients with epilepsy cannot be completely consistent given the many variables affecting the gut microbiome, namely differences in study design, age of patients, diet and living conditions. For this reason, sufficiently large samples with reasonably controlled variables are needed to obtain more accurate results.

BASIC MECHANISMS OF THE RELATIONSHIP BETWEEN GUT MICROBIOM AND EPILEPSY

As it was noted above, changes in the GMB structure are accompanied by activation of epileptic paroxysms. This most likely occurs as a result of the development of the "leaky gut" syndrome. Increased permeability of the epithelial barrier allows bacteria, toxic metabolites, endo- and exotoxins, and small molecules (inflammatory cytokines and excitatory amino acids) to enter the bloodstream, alter the integrity of the blood-brain barrier, and negatively affect the brain [55, 56]. Thus, when the integrity of these two barriers is compromised, immune cells and compounds released by microbiota enter the brain and disrupt the balance between excitatory and inhibitory neurotransmitters, provoking the development of seizures.

Gut microbes metabolise alimentary tryptophan into aryl hydrocarbon receptor agonists and interact with its receptor to control microglia activation and growth factor expression (TGFα and VEGF-B vascular growth factor), thereby modulating the pathogenic activity of astrocytes [57, 58]. Inflammatory cytokines and chemokines released by astrocytes enhance microglia activity, including phagocytosis migration of apoptotic cells and synapse contraction [59]. Contact between astrocytes and microglia increases the production of pro-inflammatory cytokines with infiltration of immune cells and subsequent chronic neuroinflammation, as well as increased blood-brain barrier permeability [60].

Microglia morphology was altered in gnotobiont- or antibiotic-treated animals. Defects in maturation, activation and differentiation of neurons were detected, which led to an inadequate immune response to various pathogens. These disorders could be eliminated only after recolonisation with microbiota [61].

In addition to glial cells, peripheral immune cells are involved in the establishment of epileptic paroxysms: T cells and monocytes that transit into brain tissue from the intestine [62]. The exact mechanism of this transit is not fully established.

GMB may provoke epilepsy through an innate immune response. Blood-brain barrier permeability has been shown to increase throughout the life of GF mice, and this is due to reduced expression of *occludin* and *claudin-5* proteins in the intestinal endothelium [63]. Intestinal dysbiosis firstly reduces claudin production and expands the permeability of the intestinal mucosa with migration of microorganisms, their metabolites and toxins from the intestinal lumen [64], and secondly, it reduces the amount of SCFAs, exacerbating blood-brain barrier permeability and generating neuroinflammation [65].

Peptidoglycan (PGN) is a component of bacterial cell wall, which is mainly present in human GI tract. But PGN is also found in brain microglia from patients with chronic encephalitis [66]. That is, PGN can move from the gut to the CNS, contributing to chronic inflammation and paroxysms.

GMB contributes to epilepsy by inducing and adaptive immunity by synthesising cytokines that penetrate the brain through the gut mucosa and the blood-brain barrier and activate immune cells in the brain to participate in the immune response. For example, *IL-17* produced by Th17 cells can be

modulated by specific phyla of the gut microbiota, primarily by *Bacteroidetes* [8, 67, 68]. It has been shown that in patients with epilepsy, both in cerebrospinal fluid and peripheral blood, *IL-17* levels are higher than in controls and have a direct correlation with the frequency and severity of seizures [69–72].

Intestinal metabolites such as SCFAs are able to influence immunoglobulin synthesis and secretion by regulating B-lymphocyte differentiation [73, 74]. The absence of a commensal microbiota suppresses *IgA* and *IgG1* formation and induces *IgE*, which increases susceptibility to disease [75, 76].

Consequently, the gut microbiota induces an immune response by initiating the gut-brain axis and accounts for epileptogenesis. In addition to the above, it can be added that an imbalance between excitatory (glutamate, dopamine, noradrenaline) and inhibitory (GABA and serotonin) neurotransmitters in the brain centre lies in the development of epilepsy [77].

Intestinal microorganisms secrete neurotransmitters that can also be generated by stimulation of intestinal cells by gut metabolites. There is evidence that the relative abundance of the genera *Coprococcus*, *Ruminococcus* and *Turicibacter* is positively correlated with glutamate and glutamine levels [78], while abundant colonisation of the gut by *A. mucinophilia* and *Parabacteroides* is able to alter amino acid levels in the intestinal lumen, serum and hippocampus in such a way as to balance the amount of seizure-related neurotransmitters, thereby providing a protective anticonvulsant effect [79].

However, the composition and structure of GMB are so complex and poorly understood that it is problematic to identify certain bacteria as the most "beneficial" or "dangerous" in epilepsy [80–82].

The most important neurotransmitter — 5-hydroxytryptamine (5-HT, serotonin) is involved in the regulation of cognitive, behavioural and other mental functions of humans. Its action is realised through 7 main families of serotonin receptors (5-HT1-5-HT7) and at least 14 subtypes, which determines their different response to specific (including pharmacological) ligands.

The main source of serotonin in the intestine is enterochromaffin cells (ECs) [83]. It is presented that patients with temporal lobe epilepsy are deficient in serotonin. However, it has been observed that fluctuations in its concentration in the gut are not able to directly affect the brain because it does not penetrate the blood-brain barrier [84]. However, 5-HT released by ECs may have a potential effect on signal transduction along the brain-gut axis, regulating afferent activity of the abdominal part of the vagus nerve [85] and inflammatory responses [86]. It has been suggested that altered levels of 5-HT in the gut are associated with epilepsy. But there is no evidence to support this.

The concentration of another neurotransmitter, N-acetylaspartic acid (NAA), is possibly decreased in patients with epilepsy. However, a pilot study found that low levels of NAA are associated with faecal *Ruminococcus faecalis* and this process is mediated by serum cortisol [87].

The role of other neurotransmitters in the pathophysiology of epilepsy is known, but it is not carried out by the gut microbiota. It has been observed that norepinephrine has a dual effect on the onset of epilepsy depending on concentration: at low doses it has a proepileptic effect, while high doses can trigger epilepsy [88].

Dopamine and acetylcholine are closely related to epilepsy and are able to indirectly influence brain function through the enteric nervous system, vagus nerve and by regulating the expression of peripheral receptors [89]. For example, acetylcholine (ACh), a major stimulant of the autonomic nervous system, activates signal transduction via cholinergic and nicotinic receptors. Accumulating evidence suggests that dysfunction of nicotinic receptors, which are widely expressed in hippocampal neurons and cortex, may be significantly involved in the pathogenesis of epilepsy. The dopamine-norepinephrine-adrenaline cycle induces hormonal and neuronal pathways. Serotonin, norepinephrine, histamine and melatonin can act as both hormones and neurotransmitters [90, 91].

THE ROLE OF FACTORS CAPABLE OF REMODELLING THE GUT MICROBIOME AND INFLUENCING THE PROGRESSION OF EPILEPSY

There is no doubt that diet, probiotics, antibiotics, and a number of other factors modify GMB composition. Recently, there is emerging work with a good evidence base that these same predictors can affect the nervous system and reduce or increase epileptic seizures.

The ketogenic diet (KD) has been successfully used to compensate for the course of a group of severe neurological diseases [92, 93] and is recommended for children as an alternative treatment for any form of epilepsy when traditionally used antiepileptic drugs are ineffective (the level of persuasiveness of recommendations is A, the level of evidence is 1) [43].

However, fundamental mechanisms of the antiepileptic effect of KD need further investigation. Current explanations are based on the operation

of neurotransmitters, brain energy metabolism, oxidative stress and ion channels [94], and microbiota remodelling [40, 95].

Adherence to classical KD for one month is accompanied by a significant decrease in total SCFAs, predominantly due to acetate, propionate and butyrate. This is due to a drastic restriction of fermentable carbohydrate intake and a decrease in the number of fermenting bacteria [96].

Some SCFAs (propionate and butyrate) have antiepileptic effects because they provide maturation of microglia of the enteric nervous system and brain and reduce the permeability of the blood-brain barrier. Butyrate improves mitochondrial dysfunction and protects brain tissue from oxidative stress and apoptosis via the Keap/Nrf2/HO-1 pathway, thereby increasing seizure threshold and reducing seizure intensity [96]. Propionate treatment can reduce seizure intensity and prolong the latency period of seizures by reducing mitochondrial damage, apoptosis, hippocampal damage and neurological deficits [97].

A 2016 systematic review presented 38 randomised controlled trials (RCTs) investigating the effects of probiotics on CNS function in both animals and humans using a specific probiotic dose and duration of administration. Three strains of bifidobacteria *(B. longum, B. breve, B. infantis)* and two strains of lactobacilli (*L. helveticus, L. rhamnosus*) were tested at doses ranging from 10^8 to 10^{10} CFU. The course of treatment was 2 weeks in animals and 4 weeks in humans. Tested probiotics have shown efficacy in the improvement of behaviour associated with psychiatric disorders such as anxiety, depression, autism spectrum disorder (ASD), obsessive-compulsive disorder, and memory recovery (spatial and non-spatial) [98].

In a prospective study of the efficacy of a probiotic mixture in patients with PRE, it was found that the frequency of seizures decreased in 28.9% of patients by more than 50%. In 76.9% of these patients, the positive effect persisted 4 months after discontinuation of treatment. This study showed that adjuvant probiotics reduce seizure frequency and can be used as an adjunctive treatment to AED [99].

In an experimental model of PTZ-induced epilepsy, a group of mice supplemented with probiotics did not develop complete kindling (epileptogenesis) due to an increase in GABA in brain tissue. Consequently, the inclusion of probiotic in the therapy significantly reduced the occurrence of sustained hyperactivity of neurons due to their profound disinhibition caused by the insufficiency of inhibitory control mechanisms and the activity of exogenous (endogenous) factors (PTZ) that caused excitation and disruption of antagonistic regulation between excitation and inhibition processes [100].

The use of synbiotic or probiotic *Lactobacillus fermentum MSK 408* in combination with KD in the treatment of PTZ-induced seizures reduced the side effects of KD without impairing its antiepileptic effects. Both KD and probiotic were found to increase GABA metabolism by regulating the gut microbiota [61].

It has been observed that saplementation of the diet of PRE patients with synbiotics enriches the GMB with SCFA-producing microorganisms [17], and *Lactobacillus fermentum MSK 408* modulates the GMB, has an effect on SCFA and restores serum lipid profile and mRNA expression of tight contact proteins in both the gut and CNS [24]. These are preliminary observations for additional probiotic effects in the treatment of PRE. It is likely that probiotics can be an adjunctive treatment for refractory epilepsy and used in combination with KD. However, further, larger placebo-controlled, experimental and clinical studies of the mechanism of action of pro- and synbiotics are needed.

Z. He et al. (2017) presented a clinical case of a young man suffering from Crohn's disease and seizures for 17 years. The patient underwent faecal microbiota transplantation for the treatment of Crohn's disease. During 20 months of follow-up, he did not record a single episode of seizures despite discontinuation of sodium valproate [101].

It was shown that treatment of newborns diagnosed rotavirus gastroenteritis with probiotics (*Saccharomyces boulardii* or *Lactobacillus casei*) reduced the risk of seizures 10-fold compared to the control group (children who did not receive probiotics). The authors suggested that *S. boulardii* suppresses paroxysmal brain activity by inhibiting the structural protein NSP4, which activates chloride channels and reactive oxygen species, or by suppressing the inflammatory response in general [102].

Six patients with PRE have been described, five of whom had complete cessation of seizures and one of whom had more than 90% reduction in seizure frequency on antibiotic (AB) treatment. After discontinuation of treatment for a fortnight, seizures recurred in all patients [103]. It is possible that such a positive effect of AB therapy is due to inhibition of the growth of one or more intestinal microorganisms responsible for the production of compounds that destroy the balance between excitation and inhibition: the main factor provoking the development of seizures. However, other mechanisms cannot be excluded.

Some ABs can cause epilepsy. For example, lactam ABs, including penicillin, cephalosporins,

and carbapenems, most commonly induce seizures [104]. IV generation of cephalosporins: imipenem and ciprofloxacin in combination with renal dysfunction, brain damage and epilepsy pose an increased risk of symptomatic seizures.

The use of ABs has short- or long-term effects on GMB composition in both humans and animals [105]. Often, ABs disrupt the balance of gut microorganisms and cause disease. Although there are ABs that increase the abundance of beneficial microorganisms and play a positive role in the structure of the gut microbiota [105].

Different groups of ABs remodelling the GMB in different ways. For example, macrolides inhibit the growth of *Actinobacteria* (mainly *Bifidobacteria)* [106, 107], oral vancomycin decreases the number of *Firmicutes* and increases the number of *Proteobacteria* [108]. Penicillin has a weak effect on human GMB [108]. The extent of amoxicillin-induced epilepsy is independent of the composition of the gut microbiota, which contradicts the hypothesis that GMB acts as a "bridge" in AB-induced epilepsy. It should be considered that the effects of AB on the microbiota are related to the initial composition of the microbiota and the habits of the macroorganism [108, 109]. In the future, a multicentre study is needed to further elucidate the specific effects and mechanisms of action of different antibiotics on epilepsy.

Antibiotics can cause the drug interactions with AEDs, which alters the operability of the last ones and consequently attenuates or enhances seizure susceptibility. Most clinically important interactions between antibiotics and AEDs result from induction or inhibition of cytochrome P450 enzymes that metabolise the drugs. This phenomenon has been widely described for carbamazepine, phenytoin, phenobarbital and rifampicin [110].

Thus, studies of microbial diversity in patients with PRE have captured that this form of the disease is often associated with the prevalence of *Firmicutes* phyla microorganisms. The use of agents (pro-, antibiotics, etc.) capable of converting GMB also converts paroxysmal brain activity in epilepsy. The study of the individual "metabolic profile" in epileptic patients when using pro- and antibiotics may possibly introduce new strategies in the treatment of this disease.

CONCLUSION

The microbiom–gut–brain axis refers to the bidirectional relationship between the gut and brain and regulates gut and CNS homeostasis through neural networks and neuroendocrine, immune and inflammatory pathways. Improvements in sequencing technology have highlighted the regulatory role of the gut microbiota in epilepsy.

Based on these findings, various means aimed at the recovery of a healthy microbial community (the diet, pre-, probiotics, antibiotics and even faecal microbiota transplantation) should be used, which may become in the near future one of the alternative treatments for the refractory epilepsy and improve the quality of life of patients suffering from this disease.

ADDITIONAL INFORMATION

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

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RELATIONSHIP OF THE GESTATIONAL AGE OF A PREMATURE NEWBORN WITH A HEREDITARY PREDISPOSITION TO METABOLIC SYNDROME

Part I. Associations of molecular genetic predictors of arterial hypertension with the gestational age of premature newborns

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Abstract. The aim of the study was to evaluate the frequency of allelic variants of the genes of predisposition to arterial hypertension in adults, depending on the gestation period of a premature newborn. The study design is prospective, controlled, single — center, non-randomized. Genomic DNA samples were studied in newborns with extremely low body weight (ELBW) and gestational age ≤28 weeks (n=95), premature newborns (NN) with gestational age >28 but ≤34 weeks (n=105), as well as a population sample of adults (n=100). For the analysis, loci with already known association with the development of arterial hypertension and coronary heart disease were selected: *AGT* (rs4762), *AGTR1* (rs5186), *ACE* (Ins\Del), *ADRB1* (rs1801253), *ADD1* (rs4961), *CYP11B2* (rs1799998), *eNOS* (rs1799983), *eNOS* (rs1549758), *eNOS* (rs2070744). The distribution of allele frequencies between the study groups was compared. Premature infants are significantly more likely to carry the allele C of the AGT gene. In newborns with ELBW, we additionally found a more frequent occurrence of mutant alleles of the *eNOS* gene and the rare GG genotype in the *ADRB1* gene. It is established that newborns with extremely low body weight, in contrast to the population of premature babies, are carriers of a greater number of risk alleles of genes predisposing to arterial hypertension.

Keywords: *premature newborns, arterial hypertension, hereditary predisposition, gene polymorphism*

ВЗАИМОСВЯЗЬ ГЕСТАЦИОННОГО ВОЗРАСТА НЕДОНОШЕННОГО НОВОРОЖДЕННОГО С НАСЛЕДСТВЕННОЙ ПРЕДРАСПОЛОЖЕННОСТЬЮ К МЕТАБОЛИЧЕСКОМУ СИНДРОМУ

Часть I. Ассоциации молекулярно-генетических предикторов артериальной гипертензии с гестационным возрастом недоношенных новорожденных

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Резюме. Цель работы — оценка частоты носительства аллельных вариантов генов, предрасположенности к артериальной гипертензии взрослых в зависимости от срока гестации недоношенного новорожденного. Дизайн исследования: проспективное, контролируемое, одноцентровое, нерандомизированное. Изучались образцы геномной ДНК у новорожденных детей с экстремально низкой массой тела (ЭНМТ) и гестационным возрастом ≤28 недель (n=95), недоношенных новорожденных (НН) с гестационным возрастом >28 но ≤34 недель (n=105), а также популяционной выборки взрослых (n=100). Для анализа были выбраны локусы с уже известной ассоциацией с развитием артериальной гипертензии и ишемической болезнью сердца: *AGT* (rs4762), *AGTR1* (rs5186), *ACE* (Ins\Del), *ADRB1* (rs1801253), *ADD1* (rs4961), *CYP11B2* (rs1799998), *eNOS* (rs1799983), *eNOS* (rs1549758), *eNOS* (rs2070744). Проводилось сравнение распределения частот аллелей и генотипов между исследуемыми группами лиц. Недоношенные дети достоверно чаще являются носителями аллеля С гена *AGT*. У новорожденных с ЭНМТ дополнительно выявлена более частая встречаемость мутантных аллелей гена *eNOS* и редкого генотипа GG гена *ADRB1*. Установлено, что новорожденные с ЭНМТ, в отличие от популяции недоношенных детей, являются носителями большего числа рисковых аллелей генов предрасположенности к артериальной гипертензии.

Ключевые слова: *недоношенные новорожденные, артериальная гипертензия, наследственная предрасположенность, полиморфизм генов*

INTRODUCTION

Analysis of data on the long-term consequences of prematurity and, in particular, the associated early chronic noncommunicable diseases such as arterial hypertension (AH) and metabolic syndrome (MS) in adulthood, is one of the urgent topics of clinical research in the last decade. Historically, the focus in the development of cardiovascular diseases emphasized individual risk factors. They were identified in the Framingham Study and other longitudinal observational projects so far [1]. The traditional risk factors are hypertension, dyslipidemia, obesity, diabetes and smoking. Subsequently, other potential predictors of AH, such as inflammation and insulin resistance, were included in this list [1]. The recognition of risk factors was a significant progress that allowed to identify real clinical targets of therapeutic interventions. Subsequent studies have shown that interventions that lead to risk factor eliminating actually reduce the risk of morbidity and mortality from cardiovascular disease [2].

At the same time, subtle mechanisms of these outcomes remain poorly understood. As applied to pediatric practice, causes related to environmental factors, various aspects of the theory of "fetal programming" and genetic features of premature infants are discussed in this aspect [3, 4].

Moreover, these data quite unambiguously point to the significance of gestational age for the early onset and even mortality from cardiovascular diseases, diabetes and lung diseases among individuals [3–7]. However, not all studies show a significant relationship between prematurity and arterial hypertension in adult individuals [6]. Although hereditary predisposition to AH may play its role in the process [7].

AIM

The aim of the research was to evaluate the frequency of carrying allelic variants of genes predisposing to adult arterial hypertension in premature newborns depending on gestational age.

MATERIALS AND METHODS

Research design: prospective, controlled, single-center, non-randomized. The research was performed on the base of the Republican Clinical

Perinatal Center of the Republic of Bashkortostan in the period from 01.02.2019 to 01.03.2020. The research was approved by the ethical committee of the State Budgetary Institution "Republican Children's Clinical Hospital" of the Ministry of Health of the Republic of Bashkortostan (Protocol No. 9 of 21.01.2019).

Genomic DNA samples were collected from neonates with extremely low birth weight (ELBW) below 1000 g and gestational age of 28 weeks or less (ELBW group; n=95); premature neonates (PN) with low birth weight less than 2000 g but more than 1000 g and gestational age less than 34 weeks but more than 28 weeks (PN group; n=105), as well as a population sample of adults from the Republic of Bashkortostan (control, n=100) (Table 1).

Molecular genetic tests were performed at the Center of Molecular Medicine of Bashkir State University, Ufa. DNA samples (repeats) isolated from peripheral blood lymphocytes of the examined neonates served as a material for the tests. The quality and quantity of isolated genomic DNA were examined using a Qubit 3.0 fluorimeter (Invitrogen, USA). Amplification was performed using reagent kits from Syntol, Russia, on a CFX96 Touch Real Time System detection amplifier (BioRad, USA). All loci were genotyped by real-time polymerase chain reaction (PCR) in the presence of fluorescent probes using Taqman technology according to the manufacturer's protocol (Syntol LLC, Russia).

The loci which were already associated with the development of arterial hypertension and coronary heart disease were selected for analysis: *AGT* (rs4762) — angiotensinogen gene, *AGTR1* (rs5186) — angiotensin II type 1 receptor gene, *ACE* (Ins/Del) — angiotensin-converting enzyme gene, *ADRB1* (rs1801253) — β1-adrenoreceptor gene, *ADD1* (rs4961) — gene of alpha-subunit of adducin protein, *CYP11B2* (rs1799998) — gene of cytochrome P450 second polypeptide, *eNOS* (rs1799983) — gene of nitric oxide synthase, *eNOS* (rs1549758), *eNOS* (rs2070744).

Statistical analysis was performed according to the "case-control" type: where "case" is a sample of ELBW or PN, "control" is a population sample. The distribution of allele and genotype frequencies between the studied groups of individuals was compared.

Hardy–Weinberg equilibrium conditions were fulfilled for all polymorphic loci studied for both cases and controls. The χ^2 method was used to calculate associations. Inheritance was estimated using a multiplicative model. If there were statistically significant differences in the distribution of allele and genotype frequencies between the study groups, calculations for the dominant and recessive models were also performed.

RESULTS

The results of the analysis of allele and genotype frequency distribution of polymorphic loci of arterial hypertension susceptibility genes in the preterm neonates are presented in Table 2.

No statistically significant differences between groups ($p > 0.05$) in polymorphic loci distribution frequencies was shown for genes *AGTR1* (rs5186), *ACE* (Ins-Del), *ADRB1* (rs1801253) gene, *eNOS* (rs1799983, rs1549758 and rs2070744), *ADD1* (rs4961), *CYP11B2* (rs1799998).

At the same time, there were statistically significant differences in the distribution of allele frequencies ($p=0.0002$) of the polymorphic locus rs4762 (Thr174Met) in the *AGT* gene between samples of preterm newborns and controls. There was performed an analysis of statistically significant differences in the frequency distribution of the homozygous recessive genotype of *AGT* (rs4762) among the studied groups. The C allele and CC genotype (according to the recessive inheritance model) were shown to be significantly more frequent in newborns with PN than in controls (84.2% vs 71% and 69.3 vs 46%, respectively) — $\chi^2=14.31$; $p=0.0002$; odds ratio 2.17; 95% confidence interval 1.45–3.26 and $\chi^2=15.33$; $p=9.0E-5$; OR 2.66; 95% CI 1.62–4.36.

Table 1. Demographic characteristics of the studied groups of children

Таблица 1. Демографические характеристики исследуемых групп детей

Показатель / Indicator	Экстремально низкая масса тела / Extremely low body weight (n=95)	Недоношенные новорожденные / Premature newborns (n=105)
Вес, г	874,7±181,86	1486,54±482,31
Рост, см	33,55±3,33	43,32±5,14
Гестационный возраст, недели	26,79±1,39	32,23±2,39

Table 2. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to arterial hypertension in the studied premature infants

Таблица 2. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к артериальной гипертензии у исследуемых недоношенных детей

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Ген AGT (rs4762) Аллель *C* / Gene *AGT* (rs4762) Allele *C*	0.842	0.710	14.31	**0.0002**	2.17	1.45–3.26
Ген AGT (rs4762) Аллель *T* / Gene AGT (rs4762) Allele *T*	0.158	0.290			0.46	0.31–0.69
Ген AGTR1 (rs5186) Аллель *A*	0.766	0.790	0.43	0.51	0.87	0.58–1.32
Ген AGTR1 (rs5186) Аллель *C* / Gene *AGTR1* (rs5186) Allele *A*	0.234	0.210			1.15	0.76–1.73
Ген ACE (Ins\Del) Аллель *I* / Gene *ACE* (Ins\Del) Allele *I*	0.540	0.585	1.08	0.3	0.83	0.59–1.18
Ген ACE (Ins\Del) Аллель *D* / Gene *ACE* (Ins\Del) Allele *D*	0.460	0.415			1.20	0.85–1.69
Ген ADRB1 (rs1801253) Аллель *C* / Gene *ADRB1* (rs1801253) Allele *C*	0.802	0.798	0.01	0.92	1.02	0.67–1.56
Ген ADRB1 (rs1801253) Аллель *G* / Gene *ADRB1* (rs1801253) Allele *G*	0.198	0.202			0.98	0.64–1.50
Ген eNOS rs1799983 Аллель *G* / Gene *eNOS* rs1799983 Allele *G*	0.770	0.750	0.30	0.58	1.12	0.75–1.66
Ген eNOS rs1799983 Аллель *T* / Gene *eNOS* rs1799983 Allele *T*	0.230	0.250			0.90	0.60–1.33
Ген eNOS rs1549758 Аллель *C* / Gene *eNOS* rs1549758 Allele *C*	0.763	0.760	0.01	0.94	1.01	0.68–1.51
Ген *eNOS* rs1549758 Аллель *T* / Gene *eNOS* rs1549758 Allele *T*	0.237	0.240			0.99	0.66–1.47
Ген *eNOS* rs2070744 Аллель *T* / Gene *eNOS* rs2070744 Allele *T*	0.676	0.725	1.51	0.22	0.79	0.54–1.15
Ген eNOS rs2070744 Аллель *C* / Gene *eNOS* rs2070744 Allele *C*	0.324	0.275			1.26	0.87–1.84
Ген *ADD1 rs4961* Аллель *G* / Gene *ADD1 rs4961* Allele *G*	0.774	0.835	2.96	0.09	0.68	0.43–1.06
Ген *ADD1 rs4961* Аллель *T* / Gene *ADD1 rs4961* Allele *T*	0.226	0.165			1.48	0.95–2.30
Ген *CYP11B2 rs1799998* Аллель *T* / Gene *CYP11B2 rs1799998* Allele *T*	0.492	0.515	0.27	0.6	0.91	0.65–1.28
Ген *CYP11B2 rs1799998* Аллель *C* / Gene *CYP11B2 rs1799998* Allele *C*	0.508	0.485			1.10	0.78–1.54

Subsequently, a comparative analysis was performed in order to note the differences between allele frequency distribution of the same genes among a population-based sample of adults and ELBW (Table 3).

Analyzing the data in Table 3, it may be noted that there were statistically significant differences in the distribution of allele frequencies (p=0.0007) of the polymorphic locus rs4762 (Thr174Met) in the *AGT* gene between the samples of ELBW and controls, which is similar to the general group of premature infants. In addition, it was found that CC genotype (according to recessive inheritance model) was significantly more frequent in ELBW

Table 3. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to arterial hypertension in the studied newborns with extremely low body weight

Таблица 3. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к артериальной гипертензии у исследуемых новорожденных с экстремально низкой массой тела

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Ген *AGT* (rs4762) Аллель *C* / Gene *AGT* (rs4762) Allele *C*	0.853	0.710	11.53	**0.0007**	2.36	1.43–3.91
Ген *AGT* (rs4762) Аллель *T* / Gene *AGT* (rs4762) Allele *T*	0.147	0.290			0.42	0.26–0.70
Ген *AGTR1* (rs5186) Аллель *A* / Gene *AGTR1* (rs5186) Allele *A*	0.805	0.790	0.14	0.71	1.10	0.67–1.80
Ген AGTR1 (rs5186) Аллель *C* / Gene *AGTR1* (rs5186) Allele *C*	0.195	0.210			0.91	0.55–1.49
Ген *ACE* (Ins\Del) Аллель *I* / Gene *ACE* (Ins\Del) Allele *I*	0.511	0.585	2.18	0.14	0.74	0.50–1.10
Ген *ACE* (Ins\Del) Аллель *D* / Gene *ACE* (Ins\Del) Allele *D*	0.489	0.415			1.35	0.91–2.02
Ген *ADRB1* (rs1801253) Аллель *C* / Gene *ADRB1* (rs1801253) Allele *C*	0.758	0.798	0.90	0.34	0.79	0.49–1.28
Ген *ADRB1* (rs1801253) Аллель *G* / Gene *ADRB1* (rs1801253) Allele *G*	0.242	0.202			1.26	0.78–2.04
Ген *eNOS* rs1799983 Аллель *G* / Gene *eNOS* rs1799983 Allele *G*	0.862	0.750	7.68	**0.006**	2.08	1.23–3.51
Ген *eNOS* rs1799983 Аллель *T* / Gene *eNOS* rs1799983 Allele *T*	0.138	0.250			0.48	0.29–0.81
Ген eNOS rs1549758 Аллель *C* / Gene *eNOS* rs1549758 Allele *C*	0.851	0.760	5.10	**0.02**	1.80	1.08–3.02
Ген *eNOS* rs1549758 Аллель *T* / Ген *eNOS* rs1549758 Аллель *T*	0.149	0.240			0.55	0.33–0.93
Ген *eNOS* rs2070744 Аллель *T* / Gene *eNOS* rs2070744 Allele *T*	0.697	0.725	0.38	0.54	0.87	0.56–1.35
Ген *eNOS* rs2070744 Аллель *C* / Gene *eNOS* rs2070744 Allele *C*	0.303	0.275			1.15	0.74–1.78
Ген *ADD1* rs4961 Аллель *G* / Gene *ADD1* rs4961 Allele *G*	0.791	0.835	1.21	0.27	0.75	0.45–1.26
Ген *ADD1* rs4961 Аллель *T* / Gene *ADD1* rs4961 Allele *T*	0.209	0.165			1.34	0.80–2.24
Ген *CYP11B2* rs1799998 Аллель *T* / Gene *CYP11B2* rs1799998 Allele *T*	0.544	0.515	0.32	0.57	1.12	0.75–1.68
Ген CYP11B2 rs1799998 Аллель *C* / Gene *CYP11B2* rs1799998 Allele *C*	0.456	0.485			0.89	0.60–1.33

than in controls (85.53% vs 71% and 70.5 vs 46%, respectively) — χ^2=11.53; p=0.0007; OR 2.36; 95% CI 1.43–3.91 and χ^2=12.03; p=0.0005; OR 2.81; 95% CI 1.56–5.07. In addition, TT genotype was more often detected in the population sample compared to ELBW (p=0.05).

Allele and genotype frequencies of polymorphic loci in genes *AGTR1* (rs5186), *ACE* (Ins-Del), *ADRB1* (rs1801253), *ADD1* (rs4961) and *CYP11B2* (rs1799998) were not statistically significant (p >0.05). At the same time, when comparing the genotype frequency distribution of the polymorphic locus in ADRB1

(rs1801253) between the studied groups, it was shown that the GG genotype, which was homozygous for a rare allele, was more frequently detected in ELBW (4.2% of cases) compared to the population control (not detected) — χ^2=4.27; p=0.04; OR 9.79; 95% CI 0.52–18.43. Statistically significant differences were found in the distribution of allele frequencies (p=0.006) and genotypes (p=0.02) of the polymorphic locus in eNOS (rs1799983) between the ELBW group and controls. The G allele was significantly more frequent in newborns with ELBW than in controls (86.2% vs 75.0%) — χ^2=7.68; p=0.006; OR 2.08; 95% CI 1.23–3.51. Whereas the T allele was significantly less frequent among newborns with ELBW compared to the population average (13.8% vs 25.0%) — χ^2=7.68; p=0.006; RR 0.48; 95% CI 0.29–0.81. The GG genotype also appeared to be more frequently detected in the ELBW group (73.4% vs 56.0) — χ^2=6.40; p=0.01; OR 2.17; 95% CI 1.18–3.97. Statistically significant differences in allele frequency distribution (p=0.02) and *eNOS* (rs1549758) were found between samples of neonates with extremely low birth weight and controls. The C allele was shown to be significantly more frequent in children with ENMT as compared to control (85.1% vs 76.0%) — χ^2=5.10; p=0.02; OR 1.80; 95% CI 1.08–3.02. Whereas the T allele was significantly less frequent among neonates with ELBW than the population average (14.9% vs 24.0%) — χ^2=5.10; p=0.02; OR 0.55; 95% CI 0.33–0.93. The CC genotype was also more frequently detected in the ELBW group (72.3% vs 57.0) — χ^2=4.98; p=0.03; OR 1.97; 95% CI 1.08–3.60.

No statistically significant differences (p >0.05) were found in distribution of allele and genotype frequencies of the polymorphic locus in eNOS (rs2070744) between groups.

DISCUSSION

The aim of the research was to determine that increased incidence of cardiovascular disease in adulthood may be related to hereditary predisposition in individuals born prematurely. In addition, gestational age was proposed to have some relevance as well as.

Indeed, it was found that preterm infants were significantly more likely to be carriers of the C allele, gene *AGT*. *AGT* encodes a protein angiotensinogen, from which angiotensin I is formed under the action of renin, which is actively involved in regulation of systemic blood pressure [8].

Moreover, the research revealed that ELBW have more pronounced features of patient's genotype predisposition to arterial hypertension. This contingent of patients also had a higher frequency of risk polymorphic alleles of *eNOS* and a rare GG genotype of *ADRB1*. *eNOS3* encodes a nitric oxide synthase enzyme, which produces nitric oxide (NO). Inhibition of NO synthase usually leads to prolonged arterial hypertension [8]. *ADRB1* is a gene of β1-adrenoreceptor, it encodes protein which is a target for beta-blockers. Therefore, the extent to which a drug helps to reduce high blood pressure partially depends on polymorphic loci of this gene [8].

On the one hand, this fact confirms the well-known paradigm that newborns with ELBW significantly differ from premature infants with normal body weight concerning their biological characteristics [9]. On the other hand, predisposition to early arterial hypertension in this contingent makes it necessary to modify approaches to strategy planning for future targeting of health care budget expenditures. In a large Swedish population-based cohort study (923,686 women) and a recent study from the USA, it was found that mothers who gave birth to preterm infants had an increased risk of cardiovascular disease in cathamnesis [10]. In addition, preterm neonates are known to have a significantly increased risk of coronary heart disease and associated mortality [11].

Indeed, our research has several limitations. It is very difficult to test the direct effect of single polymorphisms on blood pressure due to the minimal effect of each polymorphism. Assessing the joint effect of genes in relation to quantitative or qualitative phenotype, it is possible to encounter a methodological error when calculating the genetic risk index, which is defined as the total number of alleles associated with a disease [12]. It could be avoided by genome-wide association researches in preterm neonates. Ideally, such studies would have a strong contribution to analyze the monitoring of blood pressure data and endogenous influences such as cortisol levels and exogenous influences such as catecholamine dosing. This will hopefully lead to identifying the most significant genetic variants that can guide therapeutic decisions.

In addition, it should also be recalled that environmental factors may also contribute to individual clinical features of arterial hypertension. Specifics of allelic variants of polymorphic loci in ELBW parents had not been investigated in the research. Ethnic characteristics of PN had not been taken into account. Nor did we calculate the

necessary number of controls. All the above-mentioned indicates the need for further validation of the results obtained on a larger group.

CONCLUSION

The research demonstrated that neonates with extremely low birth weight, in contrast to premature neonates with normal body weight, carry a greater number of risk alleles of genes predisposing to arterial hypertension, which may increase the risk of developing AH in adulthood.

ADDITIONAL INFORMATION

Author contribution. P.I. Mironov — concept and design of the study, processing of material, writing the article, literature analysis; Yu.S. Aleksandrovich — typing and processing of material, writing the article; O.H. Nurgalieva — typing and processing of material, writing the article; R.R. Valiev— performing genetic research, processing material, writing articles, analyzing literature; A.S. Bogdanova — performing genetic research; S.G. Petrova — performing genetic research; E.K. Khusnutdinova — reviewing intellectual content; D.O. Ivanov — reviewing intellectual content. All authors read and approved the final version before publication.

Competing interests. The authors declare that they have no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. П.И. Миронов — концепция и дизайн исследования, обработка материала, написание статьи, анализ литературы; Ю.С. Александрович — набор и обработка материала, написание статьи; А.Х. Нургалиева — набор и обработка материала, написание статьи; Р.Р. Валиев — выполнение генетических исследований, обработка материала, написание статьи, анализ литературы; А.С. Богданова — выполнение генетических исследований; С.Г. Петрова — выполнение генетических исследований; Э.К. Хуснутдинова — рецензирование интеллектуального содержимого; Д.О. Иванов — рецензирование интеллектуального содержимого. Все авторы прочли и одобрили финальную версию перед публикацией.

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RELATIONSHIP OF THE GESTATIONAL AGE OF A PREMATURE NEWBORN WITH A HEREDITARY PREDISPOSITION TO METABOLIC SYNDROME

Part II. Associations of molecular genetic predictors of overweight and type 2 diabetes mellitus with the gestational age of premature newborns

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Abstract. The aim of the study was to evaluate the frequency of carrier allelic variants of polymorphic loci of genes predisposing to overweight and type 2 diabetes mellitus, depending on the gestation period of a premature newborn. The study design is prospective, controlled, single — center, non-randomized. Genomic DNA samples were studied in newborns with extremely low body weight (ELBW) and gestational age ≤28 weeks (n=95), premature newborns (PN) with gestational age >28 and ≤34 weeks (n=105), as well as a population sample of adults (n=100). For the analysis, we selected loci with a well — known association with the development of overweight and type 2 diabetes — *ADRB2* (rs1042713) and (rs1042714), *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2_IVS3* (rs7903146) and *TCF7L2_IVS4* (rs12255372), *PPARGC1A* (rs8192678), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963), *SIRT1* (rs7069102). The distribution of allele frequencies between the study groups was compared. PN are significantly more likely to be carriers of the A allele and the AA genotype of the rs8192678 locus in the *PPARGC1A* gene. In newborns with ELBW, we additionally revealed a more frequent occurrence of the C allele and the CC genotype of the rs4253778 locus in the *PPARA* gene. It is established newborns with ELBW are more frequent carriers of rare allelic variants of genes predisposing to metabolic syndrome

Key words: *premature newborns, metabolic syndrome, hereditary predisposition, gene polymorphism*

ВЗАИМОСВЯЗЬ ГЕСТАЦИОННОГО ВОЗРАСТА НЕДОНОШЕННОГО НОВОРОЖДЕННОГО С НАСЛЕДСТВЕННОЙ ПРЕДРАСПОЛОЖЕННОСТЬЮ К МЕТАБОЛИЧЕСКОМУ СИНДРОМУ

Часть II. Ассоциации молекулярно-генетических предикторов избыточной массы тела и сахарного диабета 2-го типа с гестационным возрастом недоношенных новорожденных

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Резюме. Цель работы — оценка частоты носительства аллельных вариантов полиморфных локусов генов предрасположенности к ожирению и сахарному диабету 2-го типа в зависимости от срока гестации недоношенного новорожденного. Дизайн исследования: проспективное, контролируемое, одноцентровое, нерандомизированное. Изучались образцы ДНК у новорожденных с экстремально низкой массой тела (ЭНМТ) и гестационным возрастом ≤28 недель (n=95), недоношенных новорожденных (НН) с гестационным возрастом >28 и ≤34 недель (n=105), и популяционной выборки взрослых (n=100). Для анализа были выбраны локусы с уже известной ассоциацией к развитию ожирения и сахарного диабета 2-го типа — *ADRB2* (rs1042713) и (rs1042714), *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2*_IVS3 (rs7903146) и *TCF7L2*_IVS4 (rs12255372), *PPARGC1A* (rs8192678), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963), *SIRT1* (rs7069102). Проводилось сравнение распределения частот аллелей между исследуемыми группами пациентов. НН достоверно чаще являются носителями аллеля А и генотипа АА локуса rs8192678 гена *PPARGC1A*. У новорожденных с ЭНМТ дополнительно выявлена более частая встречаемость аллели С и генотипа СС локуса rs4253778 гена *PPARA*. Установлено, что новорожденные с ЭНМТ являются более частыми носителями редких аллельных вариантов генов предрасположенности к метаболическому синдрому.

Ключевые слова: *недоношенные новорожденные, метаболический синдром, наследственная предрасположенность, полиморфизм генов*

INTRODUCTION

Incidence of preterm birth has increased significantly over the past 50 years and now affects nearly 11% of all newborns [1]. During the same period, medical advances have led to a significant improvement in the survival rate. Currently, more than 95% of premature neonates receiving modern neonatal and pediatric care survive to adulthood [2, 3]. Consequently, an unprecedented number of preterm birth survivors are now transitioning to adulthood each year (>10 million per year worldwide) [4]. This trend will have growing clinical importance. Therefore, clinicians who provide adult health care will increasingly encounter patients having undergone preterm birth. From this perspective, particularly, mechanisms and predictors of metabolic syndrome (MS), with obesity, arterial hypertension, and type 2 diabetes mellitus as its main manifestations, are being actively studied [5].

The genetic basis of MS predisposition has been poorly examined so far. There is evidence that predisposition to the disease may have hereditary nature. Although the clinical relevance of presumed genetic markers still requires convincing confirmation [6–8].

AIM

The aim of the research was to evaluate the frequency of carrying allelic variants of genes predisposing to overweight and type 2 diabetes mellitus in preterm newborns depending on gestational age.

MATERIALS AND METHODS

Research design: prospective, controlled, single-center, non-randomized. The research was performed on the base of the Republican Clinical Perinatal Center of the Republic of Bashkortostan in the period from 01.02.2019 to 01.03.2020. The research was approved by the ethical committee of the State Budgetary Institution "Republican Children's Clinical Hospital" of the Ministry of Health of the Republic of Bashkortostan (Protocol No. 9 of 21.01.2019).

Table 1. Demographic characteristics of the studied groups of children

Таблица 1. Демографические характеристики исследуемых групп детей

Показатель / Indicator	Экстремально низкая масса тела / Extremely low body weight (n=95)	Недоношенные новорожденные / Premature newborns (n=105)
Вес, г	874,7±181,86	1486,54±482,31
Рост, см	33,55±3,33	43,32±5,14
Гестационный возраст, недели	26,79±1,39	32,23±2,39

Genomic DNA samples were collected from neonates with extremely low birth weight (ELBW) below 1000 g and gestational age of 28 weeks or less (ELBW group; n=95); premature neonates (PN) with low birth weight less than 2000 g but more than 1000 g and gestational age less than 34 weeks but more than 28 weeks (PN group; n=105), as well as a population sample of adults from the Republic of Bashkortostan (control, n=100) (Table 1).

Molecular genetic tests were performed at the Center of Molecular Medicine of Bashkir State University, Ufa. DNA samples (repeats) isolated from peripheral blood lymphocytes of the examined neonates served as a material for the tests. The quality and quantity of isolated genomic DNA were examined using a Qubit 3.0 fluorimeter (Invitrogen, USA). Amplification was performed using reagent kits from Syntol, Russia, on a CFX96 Touch Real Time System detection amplifier (BioRad, USA). All loci were genotyped by real-time polymerase chain reaction (PCR) in the presence of fluorescent probes using Taqman technology according to the manufacturer's protocol (Syntol LLC, Russia).

The loci which are associated with development of MS (overweight, hyperglycemia) were selected for analysis: the beta-2-adrenergic receptor gene — *ADRB2* (rs1042713) and *ADRB2* (rs1042714), the beta-3-adrenergic receptor gene — *ADRB3* (rs4994), guanine nucleotide-binding protein beta-3 — *GNB3* (rs5443), peroxisome proliferator-activated receptor gene — *PPARA* (rs4253778), peroxisome proliferator-activated receptor protein delta gene — *PPARD* (rs2016520), T-cell transcription factor 4 gene — *TCF7L2_IVS3* (rs7903146) and *TCF7L2_IVS4* (rs12255372), peroxisome proliferator-activated receptor gamma coactivator 1-alpha gene — *PPARGC1A* (rs8192678), methylenetetrahydrofolate reductase gene — *MTHFR* (rs1801131), peroxisome proliferator-activated receptor gamma gene — *PPARG* (rs1801282), melatonin receptor 1B gene — *MTNR1B* (rs10830963), Sirtuin 1 gene — *SIRT1* (rs7069102).

Statistical analysis was performed according to the "case-control" type: where "case" is a sample of ELBW or PN, "control" is a population sample. The distribution of allele and genotype frequencies between the studied groups of individuals was compared.

Hardy–Weinberg equilibrium conditions were fulfilled for all polymorphic loci studied for both cases and controls. The χ^2 method was used to calculate associations. Inheritance was estimated using a multiplicative model. If there were statistically significant differences in the distribution of allele and genotype frequencies between the study groups, calculations for the dominant and recessive models were also performed.

RESULTS

The results of the analysis of allele and genotype frequency distribution of polymorphic loci of metabolic syndrome (MS) predisposition genes in the preterm neonates are presented in Table 2.

No statistically significant differences between groups ($p > 0.05$) in polymorphic loci distribution frequencies was shown for *ADRB2* (rs1042713, rs1042714).

In addition, no statistically significant differences between groups ($p > 0.05$) in polymorphic loci distribution frequencies was shown for genes polymorphic loci *ADRB3* (rs4994), *GNB3* (rs5443), *PPARA* (rs4253778), *PPARD* (rs2016520), *TCF7L2* (rs7903146) and *TCF7L2* (rs12255372), *MTHFR* (rs1801131), *MTNR1B* (rs10830963) and *SIRT1* (rs7069102).

No significant differences between the groups were also found in allele frequency distribution of the polymorphic locus *PPARG* (rs1801282). However, according to the dominant inheritance model, it was shown that the GG genotype was

Table 2. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to metabolic syndrome in the studied premature infants

Таблица 2. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к метаболическому синдрому у исследуемых недоношенных детей

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *A* rs1042713 в гене *ADRB2* / Allele *A* rs1042713 in the *ADRB2* gene	0.437	0.429	0.03	0.85	1.03	0.73–1.46
Аллель *G* rs1042713 в гене *ADRB2* / Allele *G* rs1042713 in the *ADRB2* gene	0.563	0.571			0.97	0.69–1.37
Аллель *C* rs1042714 в гене *ADRB2* / Allele *C* rs1042714 in the *ADRB2* gene	0.619	0.616	0.00	0.95	1.01	0.71–1.44
Аллель *G* rs1042714 в гене *ADRB2* / Allele *G* rs1042714 in the *ADRB2* gene	0.381	0.384			0.99	0.70–1.41
Аллель *T* rs4994 в гене *ADRB3* / Allele *T* rs4994 in the *ADRB3* gene	0.837	0.875	1.52	0.22	0.73	0.45–1.20
Аллель *C* rs4994 в гене *ADRB3* / Allele *C* rs4994 in the *ADRB3* gene	0.163	0.125			1.37	0.83–2.25
Аллель *T* rs5443 в гене *GNB3* / Allele *T* rs5443 in the *GNB3* gene	0.321	0.290	0.59	0.44	1.16	0.80–1.68
Аллель *C* rs5443 в гене *GNB3* / Allele *C* rs5443 in the *GNB3* gene	0.679	0.710			0.87	0.60–1.25
Аллель *G* rs4253778 в гене *PPARA* / Allele *G* rs4253778 in the *PPARA* gene	0.817	0.866	2.16	0.14	0.69	0.42–1.13
Аллель *C* rs4253778 в гене *PPARA* / Allele *C* rs4253778 in the *PPARA* gene	0.183	0.134			1.45	0.88–2.37
Аллель *A* rs2016520 в гене *PPARD* / Allele *A* rs2016520 in the *PPARD* gene	0.829	0.821	0.05	0.82	1.05	0.67–1.65
Аллель *G* rs2016520 в гене *PPARD* / Allele *G* rs2016520 in the *PPARD* gene	0.171	0.179			0.95	0.60–1.49
Аллель *C* rs7903146 в гене *TCF7L2* / Allele *C* rs7903146 in the *TCF7L2* gene	0.800	0.788	0.12	0.73	1.08	0.70–1.65
Аллель *T* rs7903146 в гене *TCF7L2* / Allele *T* rs7903146 in the *TCF7L2* gene	0.200	0.212			0.93	0.61–1.42
Аллель *G* rs12255372 в гене *TCF7L2* / Allele *G* rs12255372 in the *TCF7L2* gene	0.801	0.832	0.83	0.36	0.81	0.52–1.27
Аллель *T* rs12255372 в гене *TCF7L2* / Allele *T* rs12255372 in the *TCF7L2* gene	0.199	0.168			1.23	0.79–1.93
Аллель *G* rs8192678 в гене *PPARGC1A* / Allele *G* rs8192678 in the *PPARGC1A* gene	0.608	0.730	8.69	**0.003**	0.57	0.40–0.83
Аллель *A* rs8192678 в гене *PPARGC1A* / Allele *A* rs8192678 in the *PPARGC1A* gene	0.392	0.270			1.74	1.20–2.53
Аллель *A* rs1801131 в гене *MTHFR* / Allele *A* rs1801131 in the *MTHFR* gene	0.659	0.655	0.01	0.93	1.02	0.71–1.46
Аллель *C* rs1801131 в гене *MTHFR* / Allele *C* rs1801131 in the *MTHFR* gene	0.341	0.345			0.98	0.69–1.41
Аллель *C* rs1801282 в гене *PPARG* / Allele *C* rs1801282 in the *PPARG* gene	0.816	0.813	0.01	0.92	1.02	0.66–1.58
Аллель *G* rs1801282 в гене *PPARG* / Allele *G* rs1801282 in the *PPARG* gene	0.184	0.187			0.98	0.63–1.52

Ending of the table 2 / Окончание табл. 2

Аллели / Alleles	Случаи / Cases (n=105)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *C* rs10830963 в гене *MTNR1B* / Allele *C* rs10830963 in the *MTNR1B* gene	0.671	0.670	0.00	0.98	1.00	0.70–1.44
Аллель *G* rs10830963 в гене *MTNR1B* / Allele *G* rs10830963 in the *MTNR1B* gene	0.329	0.330			1.00	0.69–1.43
Аллель *C* rs7069102 в гене *SIRT1* / Allele *C* rs7069102 in the *SIRT1* gene	0.441	0.413	0.29	0.59	1.12	0.74–1.69
Аллель *G* rs7069102 в гене *SIRT1* / Allele G rs7069102 in the SIRT1 gene	0.559	0.587			0.89	0.59–1.35

Table 3. Comparative analysis of the distribution of allele frequencies of polymorphic loci of susceptibility genes to metabolic syndrome in studied newborns with extremely low body weight

Таблица 3. Сравнительный анализ распределения частот аллелей полиморфных локусов генов предрасположенности к метаболическому синдрому у исследуемых новорожденных с экстремально низкой массой тела

Аллели / Alleles	Случаи / Cases (n=95)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *A* rs1042713 в гене *ADRB2* / Allele *A* rs1042713 in the *ADRB2* gene	0.437	0.429	0.02	0.88	1.03	0.69–1.54
Аллель *G* rs1042713 в гене *ADRB2* / Allele *G* rs1042713 in the *ADRB2* gene	0.563	0.571			0.97	0.65–1.45
Аллель *C* rs1042714 в гене *ADRB2* / Allele *C* rs1042714 in the *ADRB2* gene	0.622	0.616	0.02	0.9	1.03	0.68–1.55
Аллель *G* rs1042714 в гене *ADRB2* / Allele *G* rs1042714 in the *ADRB2* gene	0.378	0.384			0.97	0.65–1.47
Аллель *T* rs4994 в гене *ADRB3* / Allele *T* rs4994 in the *ADRB3* gene	0.837	0.875	1.52	0.22	0.73	0.45–1.20
Аллель *C* rs4994 в гене *ADRB3* / Allele *C* rs4994 in the *ADRB3* gene	0.163	0.125			1.37	0.83–2.25
Аллель *T* rs5443 в гене *GNB3* / Allele *T* rs5443 in the *GNB3* gene	0.340	0.290	1.14	0.29	1.26	0.82–1.94
Аллель *C* rs5443 в гене *GNB3* / Allele *C* rs5443 in the *GNB3* gene	0.660	0.710			0.79	0.52–1.22
Аллель *G* rs4253778 в гене *PPARA* / Allele *G* rs4253778 in the *PPARA* gene	0.763	0.866	6.23	**0.01**	0.50	0.29–0.87
Аллель *C* rs4253778 в гене *PPARA* / Allele *C* rs4253778 in the *PPARA* gene	0.237	0.134			2.01	1.15–3.50
Аллель *A* rs2016520 в гене *PPARD* / Allele *A* rs2016520 in the *PPARD* gene	0.858	0.821	0.95	0.33	1.31	0.76–2.27
Аллель *G* rs2016520 в гене *PPARD* / Allele *G* rs2016520 in the *PPARD* gene	0.142	0.179			0.76	0.44–1.32
Аллель *C* rs7903146 в гене *TCF7L2* / Allele *C* rs7903146 in the *TCF7L2* gene	0.805	0.788	0.16	0.69	1.11	0.67–1.84
Аллель *T* rs7903146 в гене *TCF7L2* / Allele *T* rs7903146 in the *TCF7L2* gene	0.195	0.212			0.90	0.54–1.50
Аллель *G* rs12255372 в гене *TCF7L2* / Allele *G* rs12255372 in the *TCF7L2* gene	0.800	0.832	0.64	0.42	0.81	0.48–1.36
Аллель *T* rs12255372 в гене *TCF7L2* / Allele *T* rs12255372 in the *TCF7L2* gene	0.200	0.168			1.23	0.74–2.07

Ending of the table 3 / Окончание табл. 3

Аллели / Alleles	Случаи / Cases (n=95)	Контроль / Control (n=100)	χ^2	*p*	Отношение шансов / Odds ratio	
					значение	95% ДИ / 95% CI
Аллель *G* rs8192678 в гене *PPARGC1A* / Allele *G* rs8192678 in the *PPARGC1A* gene	0.626	0.730	4.81	**0.03**	0.62	0.40–0.95
Аллель *A* rs8192678 в гене *PPARGC1A* / Allele *A* rs8192678 in the *PPARGC1A* gene	0.374	0.270			1.61	1.05–2.48
Аллель *A* rs1801131 в гене *MTHFR* / Allele *A* rs1801131 in the *MTHFR* gene	0.632	0.655	0.23	0.63	0.90	0.60–1.37
Аллель *C* rs1801131 в гене *MTHFR* / Allele *C* rs1801131 in the *MTHFR* gene	0.368	0.345			1.11	0.73–1.68
Аллель *C* rs1801282 в гене *PPARG* / Allele *C* rs1801282 in the *PPARG* gene	0.796	0.813	0.19	0.67	0.90	0.54–1.48
Аллель *G* rs1801282 в гене *PPARG* / Allele *G* rs1801282 in the *PPARG* gene	0.204	0.187			1.12	0.67–1.85
Аллель *C* rs10830963 в гене *MTNR1B* / Allele *C* rs10830963 in the *MTNR1B* gene	0.671	0.670	0.00	0.98	1.00	0.70–1.44
Аллель *G* rs10830963 в гене *MTNR1B* / Allele *G* rs10830963 in the *MTNR1B* gene	0.329	0.330			1.00	0.69–1.43
Аллель *C* rs7069102 в гене *SIRT1* / Allele *C* rs7069102 in the *SIRT1* gene	0.458	0.413	1.00	0.32	1.20	0.84–1.71
Аллель *G* rs7069102 в гене *SIRT1* / Allele *G* rs7069102 in the *SIRT1* gene	0.542	0.587			0.83	0.58–1.19

significantly less frequent among PN than in controls (0.5% vs 4.0%) — χ^2=4.92; p=0.03; OR 0.12; 95% CI 0.01–1.10.

At the same time, there were statistically significant differences in the distribution of allele frequencies (p=0.0003) of the polymorphic locus rs8192678 in the *PPARGC1A* gene between samples of preterm newborns and controls. The G allele and the GG genotype (according to the dominant inheritance model) appeared to be significantly less frequent among preterm infants (60.8% vs 73% and 43.2% vs 56.0%, respectively) — χ^2=8.69; p=0.003; OR 0.57; 95% CI 0.40–0.83 and χ^2=6.15; p=0.04; OR 0.60; 95% CI 0.37–0.97. Whereas the A allele and AA genotype, according to the recessive inheritance model, were significantly more frequent among preterm neonates than the population average, χ^2=8.69; p=0.003; RR 1.74; 95% CI 1.20–2.53 and χ^2=6.15; p=0.01; RR 2.48; 95% CI 1.19–5.18.

Analysis of allele frequency distribution of polymorphic loci of the above-mentioned genes among neonates with extremely low body weight are presented in Table 3.

No significant differences between groups (p >0.05) were found in the allele and genotype frequency distribution of polymorphic locus in genes *ADRB2* (rs1042714), *ADRB3* (rs4994), *PPARD* (rs2016520), *TCF7L2* (rs7903146), and *TCF7L2* (rs12255372), *MTHFR* (rs1801131), *PPARG* (rs1801282), *MTNR1B* (rs10830963) and *SIRT1* (rs7069102).

At the same time, there were found statistically significant differences in the distribution of allele frequencies (p=0.01) and genotype frequencies (0.03) of the polymorphic locus rs4253778 in the *PPARA* gene between the samples of neonates with ELBW and the comparison group. The G allele and the GG genotype (according to the dominant inheritance model) appeared to be significantly less frequent among ELBW than in controls (76.3% vs 86.6% and 55.1 vs 74.2%, respectively) — χ^2=6.23; p=0.01; OR 0.5; 95% CI 0.29–0.87 and χ^2=7.00; p=0.008; OR 0.43; 95% CI 0.23–0.81. The C allele was more frequently detected among ELBW, χ^2=6.23; p=0.01; OR 2.01; 95% CI 1.15–3.50.

There were revealed statistically significant differences in the allele frequency distribution (p=0.03) of the polymorphic locus rs8192678 in the *PPARGC1A* gene between the samples of ELBW and controls. The G allele was significantly less frequent among ELBW than in the control group (62.6% vs 73.0%) — χ^2=4.81; p=0.03; OR 0.62; 95%

CI 0.40–0.95. Whereas the A allele was significantly more frequently detected among ELBW than the population average (37.4% vs 27.0%) — χ^2=4.81; p=0.03; OR 1.61; 95% CI 1.05–2.48.

DISCUSSION

The study is devoted to the search for genetic risk factors of metabolic syndrome development which are associated with prematurity. Preterm infants are significantly more likely to carry allele A and homozygous genotype AA of the polymorphic locus in *PPARGC1A* (rs8192678). The gene is responsible for the production of protein coactivator 1-alpha-receptor, which is involved in the metabolism of muscle tissues, fats and carbohydrates [11].

Allele C and genotype CC of the polymorphic locus rs4253778 in the *PPARA* gene were also significantly more frequent in ELBW. PPARα receptor is one of the subtypes of cell nucleus receptors activated by Peroxisome Proliferator Activated Receptor (PPAR), which regulates lipid metabolism in the liver and skeletal muscles, as well as glucose homeostasis [9].

To some extent, the data obtained may indicate that premature newborns have some genetic predisposition to the development of metabolic syndrome. Moreover, this is more significant when the gestational age is less than 28 weeks. A number of independent studies conducted in recent years confirm our data [10–12].

The research has a few methodological limitations. These are, first of all, the relatively small number of patients, single-center design and lack of randomization. Another limitation is the fact that it was a single-stage study and not a longitudinal one. Therefore, the significance of the identified risk factors for metabolic syndrome remains relatively uncertain.

CONCLUSION

The research demonstrated that neonates with extremely low birth weight, in contrast to premature neonates with normal body weight, as a rule, carry a greater number of rare alleles of genes predisposing to metabolic syndrome, which may increase the risk of developing MS in adulthood.

The presented data allows us to assume that the impact of unfavorable environmental factors in development of MS may have a greater effect in neonates with ELBW. Moreover, individuals born earlier than 28 weeks of gestation are more predisposed to MS due to genetic risks, in addition to the factors described in the framework of the "fetal programming" theory.

ADDITIONAL INFORMATION

Author contribution. P.I. Mironov — concept and design of the study, processing of material, writing the article, literature analysis; Yu.S. Aleksandrovich — typing and processing of material, writing the article; O.H. Nurgalieva — typing and processing of material, writing the article; R.R. Valiev — performing genetic research, processing material, writing articles, analyzing literature; A.S. Bogdanova — performing genetic research; S.G. Petrova — performing genetic research; E.K. Khusnutdinova — reviewing intellectual content; D.O. Ivanov — reviewing intellectual content. All authors read and approved the final version before publication.

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MARKERS OF ACUTE KIDNEY INJURY IN CRITICALLY ILL PRETERM NEONATES

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Abstract. Early diagnosis of acute kidney injury (AKI) in very low birth weight (VLBW) and extremely low birth weight (ELBW) preterm infants is a serious problem due to the lack of specific clinical manifestations, metabolic features, immaturity of the renal tubular and tubule apparatus, and the intensive therapy provided. The aim of the study is to compare the diagnostic value of classical markers of AKI(diuresis and serum creatinine) and other biochemical parameters (serum cystatin C and urine b2-microglobulin) in children of this group in critical condition. A total of 100 neonates with VLBW and ELBW were included in the study, 28 of whom developed AKI during the first week of life (main group). Oliguria did not develop in any child, and a diagnostically significant increase in serum creatinine was noted on the third day of life. An increase in serum creatinine and urine b2-microglobulin levels in children of the main group compared to the comparison group was detected already on the first day, which allows us to consider them more sensitive markers. However, the reference values of the indicators in children with VLBW and ELBW need to be clarified.

Key words: *acute kidney injury, creatinine, cystatin C, urine b2-microglobulin, preterm neonate, very low birth weight, extremely low birth weight*

МАРКЕРЫ ОСТРОГО ПОВРЕЖДЕНИЯ ПОЧЕК У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ В КРИТИЧЕСКОМ СОСТОЯНИИ

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Резюме. Ранняя диагностика острого повреждения почек (ОПП) у недоношенных с очень низкой (ОНМТ) и экстремально низкой массой тела (ЭНМТ) представляет собой серьезную проблему вследствие отсутствия специфических клинических проявлений, особенностей метаболизма, незрелости клубочкового и канальцевого аппарата почек, а также проводимой интенсивной терапии. Целью работы является сравнение диагностической ценности классических маркеров ОПП (диурез и сывороточный креатинин) и других биохимических показателей (сывороточный цистатин С и b2-микроглобулин мочи) у детей данной группы в критическом состоянии. В исследование были включены 100 новорожденных с ОНМТ и ЭНМТ, у 28 из которых развилось ОПП в течение первой недели жизни (основная группа). Олигурия не развилась ни у одного ребенка, диагностически значимое повышение сывороточного креатинина отмечалось на третьи сутки жизни. Увеличение уровня сывороточного цистатина С и b2-микроглобулина мочи у детей основной группы по сравнению с группой сравнения определялось уже в первые сутки, что позволяет считать их более чувствительными маркерами. Однако референсные значения показателей у детей с ОНМТ и ЭНМТ нуждаются в уточнении.

Ключевые слова: *острое повреждение почек, креатинин, цистатин С, b2-микроглобулин, недоношенный новорожденный, очень низкая масса тела при рождении, крайне низкая масса тела при рождении*

INTRODUCTION

Neonates with very low birth weight (VLBW) and extremely low birth weight (ELBW) are one of the most challenging groups of patients in intensive care units (ICU), requiring modern methods of respiratory and drug therapy, enteral and parenteral nutrition, careful monitoring and care [1]. At the same time, about 87% of premature neonates with VLBW and ELBW receive at least one nephrotoxic drug during hospitalization [2]. Asphyxia is another common factor in the development of the acute kidney injury (AKI) in preterm neonates, leading to AKI in 30–56% of cases [3, 4]. In addition, nephron development is not completed until 32–36 weeks of gestation, so the number of nephrons in extremely premature neonates is lower compared to premature neonates [5], which also predetermines the higher incidence of AKI. Various authors estimate that up to 50% of infants in ICUs have at least one episode of AKI [7], which, in turn, is an independent risk factor for morbidity and mortality in preterm neonates [8, 9].

Diagnosis of acute kidney injury in neonates with VLBW and ELBW is difficult due to non-specificity of symptoms, rapid development of decompensation, and the lack of generally accepted parameters for extremely premature neonates [6]. Currently, the KDIGO classification or its modified version pKDIGO, based on the assessment of serum creatinine level and diuresis rate, can be used to diagnose AKI [10].

The question of whether this classification can be used in preterm neonates remains debatable [11]. It is known that creatinine concentration can be affected by the catabolic orientation of metabolic processes, increased protein load, maternal creatinine level, the presence of hyperbilirubinaemia, and the method of testing [12]. In addition, diuresis in preterm newborns is influenced by their physiological tendency to polyuria and infusion therapy [13].

Serum cystatin C and urine b2-microglobulin can be used as alternative markers for AKI diagnosis. Cystatin C is a specific marker of renal tubular damage [14, 15]. Urine b2-microglobulin concentration reflects the functional status of tubules [16].

AIM

To compare the diagnostic value of serum creatinine levels and diuresis rate with serum cystatin C and urine b2-microglobulin levels for early diagnosis of acute kidney injury in critically ill premature neonates with VLBW and WLBW in the early neonatal period.

MATERIALS AND METHODS

This research was approved by the ethics committee of the Federal State Budgetary Educational Institution of Higher Professional Education "Volga Region Research Medical University" of the Ministry of Health of Russia. It is a primary prospective, non-randomized study. The research was carried out on the basis of the neonatal intensive care unit of the State Budgetary Institution of Neonatal Clinical Hospital No. 40 "Regional Perinatal Centre". The study included 100 premature newborns selected according to the following criteria: prematurity, birth weight less than 1500 g, absence of congenital malformations of the cardiovascular and genitourinary systems, life expectancy more than 168 hours, and informed voluntary parental consent for participation in the study.

28 patients were diagnosed with AKI regarding pKDIGO critera. They formed the main group.

72 patients had no signs of AKI in the early neonatal period (comparison group).

Median weight of the examined neonates was 990 [820–1250] grams. The gestational age was 28 [27–30] weeks. The median APGAR score at the 1st minute was 4 [3–5] points, and 6 [5–6] at the 5th minute. All patients required respiratory support to varying degrees. 29 patients used nCPAP as respiratory therapy, 63 patients required ventilatory support and 8 patients required high-frequency oscillatory ventilation (HFOV).

Table 1 demonstrates characteristics of the main group (patients with AKI) and the comparison group (patients without diagnosed AKI).

All patients underwent necessary laboratory and diagnostic tests on the 1st, 3rd, and 7th day of life according to internal protocols of the clinical department. Blood sampling for biochemical analysis was taken in morning hours. Peripheral vein blood was taken by means of a disposable sterile vacuum tube with a clot activator. Determination of serum creatinine was performed on a MINDRAY BS-240pro apparatus. The remaining biological samples (serum, urine) were used for determination of cystatin C and b2-microglobulin. The examination was performed on a Thermo Scientific Konelab PRIME 60 analyzer. No additional blood and urine sampling was taken.

Statistical processing of the obtained data was performed by means of IBM SPSS Statistics v.26.0 and Prism 9 (Graphpad) software package. The obtained data was evaluated for conformity to the law of normal distribution in order to choose a method of parametric analysis. Kolmogorov–Smirnov criterion was used which is recommended when the number of subjects is more than 60. In addition, the Fisher's F-criterion was calculated to assess homoscedasticity of dispersions of the obtained data, which is one of the conditions for applicability of parametric analysis methods as well. According to the data obtained, all the compared distributions differed from the normal one; therefore, non-parametric analysis methods were used. In addition, asymmetry and kurtosis indices were estimated, which also confirmed the distribution was non-normal.

The data of descriptive statistics are presented in the form of Me [Q1; Q3], where Me is the median, Q1 and Q3 are the first (25%) and third (75%) quartiles, respectively. In this case, non-parametric Mann-Whitney U-test was used in assessing statistical significance of differences between two

Table 1. Characteristics of patients in the main group and comparison group

Таблица 1. Характеристика пациентов основной группы и группы сравнения

Показатели / Indicators	Основная группа / Main group (n=28)	Группа сравнения / Comparison group (n=72)	p
Вес при рождении, г / Birth weight, g	990,0 [810,0–1100,0]	1145,0 [945,0–1340,0]	**p=0,008***
Длина тела при рождении, см / Body length at birth, cm	35,0 [31,5–38,0]	37,0 [34,5–40,0]	**p=0,014***
Срок гестации / Gestation period	26,50 [25,00–28,50]	29,00 [27,50–31,00]	**p=0,001***
Тяжелая асфиксия (оценка по APGAR 3 и менее на 1-й минуте) (абс., %) / Severe asphyxia (APGAR score 3 or less at 1st minute) (abs., %)	9 (32,1%)	15(20,8%)	0,234
Инвазивная ИВЛ (абс., %) / Invasive AVL (abs., %)	25 (89,3%)	46 (63,9%)	**0,012* OR=6,32**
Инотропная поддержка (абс., %) / Inotropic support (abs., %)	13 (46,4%)	17 (23,6%)	**0,025* OR=4,99**
ЭНМТ (абс., %) / ELBM (abs., %)	20 (71,4%)	26 (36,1%)	**0,001* OR=0,226**
Дотация СЗП (абс., %) / FFP subsidy (abs., %)	4 (14,3%)	6 (8,3%)	0,449
Иммунотерапия (абс., %) / Immunotherapy (abs., %)	6 (21,4%)	18 (25%)	0,401

* Значения статистически значимые. / Values are statistically significant.

Примечание: ИВЛ — искусственная вентиляция легких; СЗП — свежезамороженная плазма; ЭНМТ — экстремально низкая масса тела.

* Values are statistically significant.

Note: AVL — artificial lung ventilation; ELBM — extremely low body weight; FFP — fresh frozen plasma

independent samples. In this case, nonparametric Mann-Whitney U-criterion was used to assess statistical significance of differences between two independent samples. Friedman criterion was used for "before-after" studies (when studying indices of OPP markers in dynamics on the 1st, 3rd, and 7th days) which is a nonparametric analog of repeated-measures analysis of dispersion. Nominal data were compared using Pearson's χ^2 criterion. Odds Ratio (OR) was used as a quantitative measure when comparing relative indices. OR is defined as the ratio of the probability (odds) of an event occurring in a group exposed to a risk factor to the probability of an event occurring in the control group.

Differences were considered statistically significant at a significance level of $p < 0.05$.

Since b2-microglobulin is supposed to be one of the main diagnostically important markers, the sample size of patients was based on the b2-microglobulin data. Required number of patients for comparing b2-microglobulin levels depending on AKI was determined by Lehr's formula for average values (at a given research power of 90%) and by the formula for calculating the sample size when comparing two averages.

The value of the minimal clinically significant difference of b2-microglobulin concentration in urine of patients with and without AKI as well as standard deviation (3.4) was substituted into the formula. The value was determined from the pilot study involving 20 patients, it was equal to 3.69 mg/L. Thus, the minimum sample size was calculated, which amounted to 19 patients for each group (main and comparison groups), so the sample size of 100 patients is sufficient.

RESULTS

Acute kidney injury was detected in 28 preterm neonates participating in the research. Newborns with AKI were significantly more frequently diagnosed with ELBW (p=0.001, OR=0.226), and had shorter gestational age (26.50 [25.00–28.50], (p=0.001)). The severity of their condition required more intensive care: artificial lung ventilation (ALV) in 89.3% (p=0.012, LS=6.32), inotropic support in 46.4% of cases (p=0.025, LS=4.99).

Commonly accepted criteria of AKI (diuresis and serum creatinine levels), as well as serum cystatin C and urine b2-microglobulin values were analyzed in dynamics (Table 2).

Diuresis remained normal in both groups, significantly increasing by the end of the early neonatal period. No cases of oliguria were observed. Meanwhile, all newborns received infusion therapy from the first day of life in accordance with clinical recommendations. In case of haemodynamic instability, drugs with inotropic action (mainly dopamine at a starting dose of 4–5 mcg/kg per minute) were prescribed.

The same children from the main group showed increased laboratory markers during the first week. However, timing and values of the first increase differed (Table 3).

However, there is no definite agreement on the normal value of serum creatinine in extremely premature neonates. In case of preterm newborns, the normal value of serum creatinine is less than 45 μmol/l, whereas normal values for neonates with a gestational age of less than 32 weeks are considered to be higher than 120 μmol/l [17].

Therefore, dynamics is most important for diagnosing AKI, i.e., the increase in creatinine level in

Table 2. Diuresis dynamics (ml/kg/h)

Таблица 2. Динамика диуреза (мл/кг/час)

Группа пациентов / Patient group	1-е сутки / 1st day	3-и сутки / 3rd day	7-е сутки / 7th day	p
Основная группа / Main group (n=28)	3,10 [2,55–4,15]	5,00 [4,50–5,80]	5,70 [4,20–6,40]	**<0,001*** p_{1-2}=0,001 p_{2-3}=0,419 p_{1-3}<0,001
Группа сравнения / Comparison group (n=72)	3,75 [2,79–4,30]	4,95 [4,40–5,45]	5,65 [5,25–6,50]	**<0,001*** p_{1-2}<0,001 p_{2-3}=0,007 p_{1-3}<0,001

* Значения статистически значимые.

* Values are statistically significant.

Table 3. Dynamics of serum creatinine level (μmol/l)

Таблица 3. Динамика уровня сывороточного креатинина (мкмоль/л)

Группа пациентов / Patient group	1-е сутки / 1st day	3-и сутки / 3rd day	7-е сутки / 7th day	p
Основная группа / Main group (n=28)	38,00 [28,00–42,50]	91,00 [70,00–103,00]	124,50 [79,00–155,00]	**<0,001*** p_{1-2} <0,001 p_{2-3}=0,001 p_{1-3} <0,001
Группа сравнения / Comparison group (n=72)	42,50 [33,50–46,50]	57,00 [52,00–70,0]	52,50 [41,00–67,50]	0,155

* Значения статистически значимые.

* Values are statistically significant.

Table 4. Serum Cystatin C level (ng/ml)

Таблица 4. Уровень сывороточного цистатина С (нг/мл)

Группа пациентов / Patient group	1-е сутки / 1st day	3-и сутки / 3rd day	7-е сутки / 7th day	p
Основная группа / Main group (n=28)	1,85 [1,72–2,02]	2,06 [1,74–2,16]	2,27 [2,07–2,66]	**<0,001*** p_{1-2} <0,001 p_{2-3} <0,001 p_{1-3} <0,001
Группа сравнения / Comparison group (n=72)	1,57 [1,34–1,94]	1,52 [1,32–1,90]	1,84 [1,40–2,12]	**<0,001*** p_{1-2} <0,001 p_{2-3}=0,014 p_{1-3} <0,001

* Значения статистически значимые.

* Values are statistically significant.

relation to the basal one. This approach is common for all classifications of acute kidney injury.

Serum creatinine levels did not exceed 50 μmol/l in all patients on the first day. Controls had even a slightly higher creatinine level. Serum creatinine increased on average 2.5-fold by the third day of life, and by the end of the first week of life — 3-fold in controls. Serum creatinine remained stable in the comparison group.

Dynamics of serum cystatin C levels showed a different pattern (Table 4).

The cystatin C level was significantly higher in the main group as early as on the first day of life. Moreover, its values increased significantly in dynamics. At the same time, reference intervals of serum cystatin C, according to the literature, are 1.34–2.57 mg/l for premature newborns and 1.36–2.23 mg/l for full-term newborns [19].

Urine b2-microglobulin study was used to diagnose tubule abnormalities (Table 5).

Similar changes were also shown in the study of b2-microglobulin level. However, the differences between the main group and the comparison group were even more significant, and the dynamics within the group during the first week of life were less pronounced.

At the same time, the literature data on the level of b2-microglobulin in newborns are also limited. The level of b2-microglobulin equal to 1.5+0.8 mg/L at the age of 1–2 days and 1.8+0.3 mg/L at the age of 3–5 days in healthy newborns is considered normal [20]. Marker levels in extremely premature neonates must be clarified.

ROC-analysis was performed to determine the diagnostic significance of renal damage markers with the determination of sensitivity and specificity of the models, as well as separating values for each marker on the 1st, 3rd, and 7th day.

According to ROC-analysis, the creatinine level can be considered prognostically significant for AKI development not earlier than the third day of life. The area under the curve was 0.313; 0.824 and 0.924 on the 1st, 3rd, 7th day, respectively. The sensitivity of the models on the 3rd, 7th day was 75 and 71.4%, specificity was 72.2 and 72%. Separation value: 70.5 μmol/L; 92.5 μmol/L. Fig. 1 shows the results of ROC-analysis.

Table 5. Urine b2-microglobulin level (mg/L)

Таблица 5. Уровень b2-микроглобулина (мг/л)

Группа пациентов / Patient group	1-е сутки / 1st day	3-и сутки / 3rd day	7-е сутки / 7th day	p
Основная группа / Main group (n=28)	6,24 [4,16–11,56]	6,66 [4,58–11,45]	6,90 [5,33–12,50]	**<0,001*** p_{1-2}=0,053 p_{2-3}<0,001 p_{1-3}=0,003
Группа сравнения / Comparison group (n=72)	2,55 [1,05–5,65]	4,27 [0,95–15,90]	2,33 [0,94–6,92]	**0,026*** p_{1-2}=0,808 p_{2-3}=0,004 p_{1-3}=0,273

* Значения статистически значимые.
* Values are statistically significant.

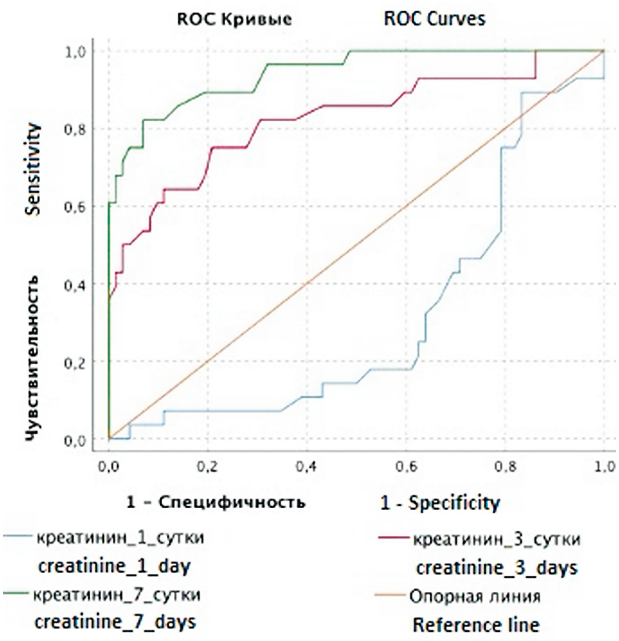

Fig. 1. ROC-curve of the prognostic significance of creatinine level at 1, 3 and 7 days of life in the diagnosis of AKI

Рис. 1. ROC-кривая прогностической значимости уровня креатинина на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

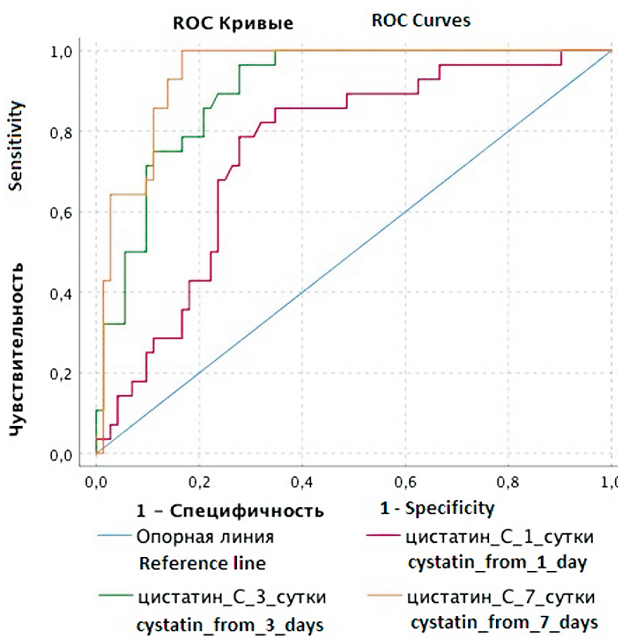

Fig. 2. ROC-curve of the prognostic significance of cystatin C levels at 1, 3 and 7 days of life in the diagnosis of AKI

Рис. 2. ROC-кривая прогностической значимости уровня цистатина С на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

When examining the diagnostic significance of cystatin C level, the area under the curve on the 1st, 3rd, and 7th days was 0.751, 0.901, and 0.943, respectively. The sensitivity of the models was 78.6, 82.1, and 92.9%. The specificity was 70.8, 79.2 and 86.1%. The separating value was 1.663 ng/mL; 1.733 ng/mL; 2.006 ng/mL. The result is presented in Fig. 2.

When examining the diagnostic significance of b2-microglobulin level, the area under the curve on the 1st, 3rd, 7th day was 0.725, 0.720, and 0.817, respectively. The sensitivity of the models was 60.7, 71.4, 82.1%. The specificity was 63.9, 62.5, 70.8%. The separating value was 4.638 mg/L; 5.245 mg/L; 5.280 mg/L. The obtained ROC curve is shown in Fig. 3.

According to the results of ROC-analysis, we can conclude that the most significant markers for the diagnosis of AKI starting from the first day of life are cystatin C and b2-microglobulin. Moreover, their diagnostic significance increases by the 7th day of life.

DISCUSSION

The number of patients diagnosed with acute kidney injury amounted to 28% in the research,

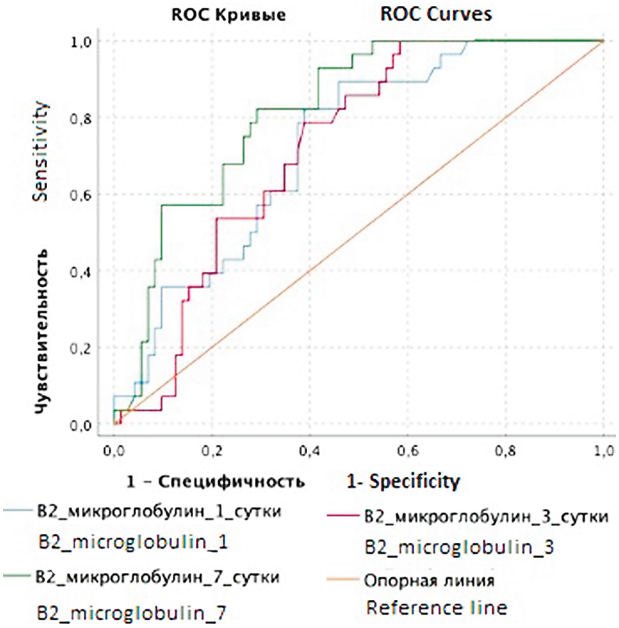

Fig. 3. ROC-curve of the prognostic significance of b2-microglobulin levels on days 1, 3 and 7 of life in the diagnosis of AKI

Рис. 3. ROC-кривая прогностической значимости уровня b2-микроглобулина на 1-е, 3-и, 7-е сутки жизни в диагностике ОПП

which does not exceed the average percentage of patients with AKI in other studies.

This pathology was more frequently detected in neonates with severe prematurity and birth weight less than 1000 g. It confirms the higher vulnerability and low compensatory capacity of kidneys due to morphological and functional immaturity, as well as the presence of a smaller number of functioning tubules. This group of patients also required more intensive therapy: invasive respiratory support, including high-frequency oscillatory ventilation, and inotropic drugs to maintain stable hemodynamics. The obtained data are consistent with the results of other studies [21], which revealed a close relationship between the progression of respiratory failure and the development of AKI in premature neonates. Acute injury makes a significant contribution to the development of multi-organ dysfunction syndrome.

All examined premature neonates did not show oliguria in the early neonatal period. Taking into account an inotropic drug which was added to treatment in case of hemodynamic instability, adequate renal blood flow and, accordingly, glomerular filtration were preserved. Similarly, the persistent high rate of diuresis in the early neonatal period might be associated with reduced water reabsorption at the tubule apparatus. The results obtained indicated that diuresis had a low significance in diagnosing AKI in premature neonates in the first 7 days of life.

The levels of serum creatinine, serum cystatin C, and b2-microglobulin in urine were increased in the same patients at different periods of time. Thus, each laboratory parameter can be used to diagnose AKI in premature neonates, since it can reflect the damage of both the glomerular and tubule renal apparatus. The absence of generally accepted reference intervals for creatinine, cystatin C, and b2-microglobulin in preterm infants does not allow us to assume AKI. It is necessary to assess the increase of markers in dynamics in case of a single study. Creatinine had the lowest sensitivity among the markers analyzed in the research: its increase was detected in all premature neonates with AKI by the 7th day of life. Cystatin C and b2-microglobulin showed higher sensitivity. Determination of b2-microglobulin in urine should also be emphasized. Its concentration of was significantly higher in the main group starting from the first day of life, and it intensively increased in dynamics by the 7th day of life. No blood sampling is required for b2-microglobulin determination, which is especially important for patients with VLBW and ELBW.

CONCLUSION

1. Acute kidney injury. According to KDIGO criteria it was diagnosed in 28% of very low and extremely low birth weight infants in critical condition in the first week of life.

2. All patients in our study had non-oliguric AKI.

3. Cystatin C, creatinine and b2-microglobulin were increased in the same newborns with AKI, indicating pathological involvement of both glomerular and tubule renal apparatus.

4. Increase of serum creatinine in relation to basal creatinine. It started on the 3rd day of life in neonates with AKI.

5. Increase in serum cystatin C and urine b2-microglobulin levels in the main group in the first day of life and its subsequent growth allow to consider them as sensitive AKI markers.

6. It is necessary to determine normal levels of serum creatinine, cystatin C, and b2-microglobulin in premature infants with extremely low and very low birth weight in order to use them more effectively in the diagnosis of AKI.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

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THE INFLUENCE OF MATERNAL OBESITY ON THE PHYSICAL DEVELOPMENT OFFSPRING IN THE FIRST YEAR OF LIFE

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Abstract. Obesity is a serious medical and social problem of modern health care system. The problem of maternal obesity associated with gynaecological, perinatal risks and risk of developing diseases in offspring. It has been proven that excess body weight before pregnancy is a significant risk factor for the development of obesity and metabolic syndrome in children. The article presents data from an analysis of physical development in children in the first year of life born to obese mothers.

Keywords: *physical development, children, maternal obesity, excess body weight*

ВЛИЯНИЕ МАТЕРИНСКОГО ОЖИРЕНИЯ НА ФИЗИЧЕСКОЕ РАЗВИТИЕ ПОТОМСТВА В ПЕРВЫЙ ГОД ЖИЗНИ

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Резюме. Ожирение является серьезной медико-социальной проблемой современного здравоохранения и достигает в мире масштабов эпидемии. Проблема материнского ожирения связана как с акушерско-гинекологическими и перинатальными рисками, так и с долгосрочным влиянием материнского ожирения на состояние здоровья потомства. Доказано, что избыточная масса тела до беременности является существенным фактором риска развития ожирения и метаболического синдрома у детей. В статье представлены данные анализа физического развития у детей, в первый год жизни, рожденных от матерей с ожирением.

Ключевые слова: *физическое развитие, дети, материнское ожирение, избыточная масса тела*

INTRODUCTION

Obesity is a serious medical and social problem of modern public health. It is reaching epidemic proportions worldwide. According to the World Health Organization (WHO) report on obesity in Europe for 2022, about 55.5% of the adult population is overweight and obese [1]. The incidence of obesity among women of childbearing age is also

steadily increasing [1]. This trend is currently the most alarming, as numerous studies have proven the role of maternal obesity in the development of complications of pregnancy and childbirth, such as habitual miscarriage, preeclampsia, gestational diabetes mellitus, gestational arterial hypertension, weak labor, increased incidence of operative delivery, bleeding in labor and early postpartum, traumatic injuries in the mother and fetus, infections in the area of surgical interventions, and intrauterine retention [2–4]. Besides complications of pregnancy, childbirth and perinatal risks, the long-term effects of maternal obesity are actively studied. It has been proved that excessive body weight before pregnancy is a significant risk factor for the development of obesity and metabolic syndrome in offspring [5, 6]. Analysis of 2416 population studies revealed that from 1975 to 2016, there was an increasing trend in BMI in children and adolescents [7]. Childhood obesity, in turn, is associated with the risk of developing diseases in adulthood, such as metabolic syndrome, cardiovascular and musculoskeletal diseases, atopic dermatitis, type 2 diabetes mellitus, and the development of psychological problems [8–11].

AIM

To analyze the dynamics of physical development in children in the first year of life born to obese mothers.

MATERIALS AND METHODS

90 children were included in the study: Group 1 — 54 children from obese mothers (mother's body mass index (BMI) before pregnancy ≥30 kg/m^2; Group 2 — 36 children from mothers with normal BMI (18.5–24.9 kg/m2). The mean maternal BMI at the time of delivery in group 1 was 38.1 kg/m^2 and in group 2 was 22.7 kg/m^2. The number of children born through natural labor was 66.1%, and by cesarean section — 33.9%. The number of premature neonates in the groups was 4.6%, and 95.4% neonates were full-term. The average gestational age of newborns was 39 weeks in both groups. Girls accounted for 46.8%, boys — 53.2% in the studied groups.

Anthropometric parameters were assessed at birth according to sex and gestational age using INTERGROWTH-21st standards [12]. The INTERGROWTH-21 scale (size at birth charts) was developed on the basis of data obtained by measuring weight, body length, and head circumference in healthy newborns of different gestational ages (33–42 weeks). Parameters within ±1 SD were evaluated as a variant of mean values. Deviations which were more or less than 1 SD from the median were evaluated as "above average" and "below average", respectively.

All children were assessed for anthropometric parameters every month. These parameters were further analyzed by sex and age according to WHO standards for children by means of the WHO Anthro program. Anthropometric parameters were assessed in standard deviations from the mean (SDS — standard deviation score). Parameters within ±1 SD were evaluated as a variant of mean values. Deviations which were more or less than 1 SD from the median were evaluated as "above average" and "below average", respectively. Body mass index (BMI), which is calculated as the ratio of body weight in kilograms (kg) to the square of body length expressed in meters (m^2), is the most informative method since it is difficult to determine the amount of body fat directly. BMI has been shown to correlate with the amount of body fat in both adults and children. BMI was calculated according to the standards for a particular age and sex and was presented as the number of standard deviations from the mean (SDS).

Statistical processing of the material was carried out using standard methods of mathematical statistics and IBM SPSS Statistics 26 software package. Description of quantitative data was presented in the form of sample mean standard deviation and 95% confidence interval in the form of M±σ (95% CI) in case hypothesis of normal distribution is accepted. If this hypothesis was rejected, median (Me) and quartiles of Q1 and Q3 were presented in the format Me (Q1; Q3). The Shapiro–Wilk and Kolmogorov–Smirnov criteria were used to test the hypothesis of normal distribution. The Student's criterion (with Welch's correction if there were different dispersions) was used to compare independent samples. Absolute value and relative value in percentage were specified for qualitative indicators. Qualitative attributes of the groups were compared using Pearson's χ^2 criterion. The results were considered statistically significant at the $p < 0.05$ level.

RESULTS

The research analyzed the dynamics of somatometric indicators and harmony of physical development in children born to obese mothers compared to children born to mothers with nor-

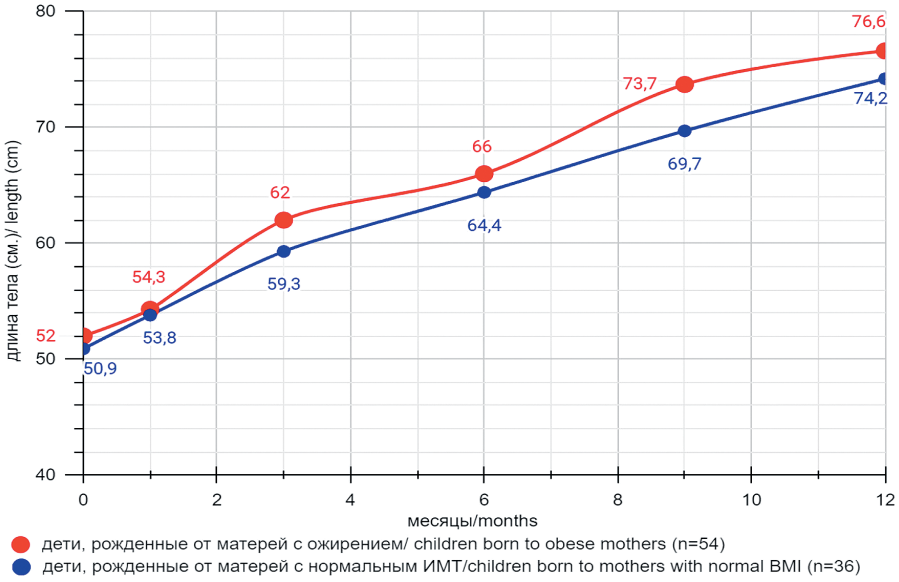

Fig. 1. Dynamics of body length in groups of children born to obese women and women with normal body mass index (BMI) (hereinafter in figure captions)

Рис. 1. Динамика длины тела в группах детей, рожденных женщинами с ожирением и женщинами с нормальным индексом массы тела (ИМТ) (здесь и далее в подрисуночных подписях)

Table 1. Increases in body length (cm) in examined children in 2 groups during the observation period

Таблица 1. Прибавки длины тела (см) у обследованных детей в 2 группах за период наблюдения

Прибавки длины тела в группах (см) / Increases in body length in groups (cm)	Период, месяцы / Period, months				
	0–1	1–3	3–6	6–9	9–12
Дети от матерей с ожирением / Children of obese mothers	2,3±0,2	7,7±0,4	4,0±0,2	7,5±02	2,9±0,1
Дети от матерей с нормальным ИМТ / Children from mothers with normal BMI	2,9±0,4	5,2±0,4	5,1±0,1	5,2±0,3	4,9±0,2
Примечание / Note	p=0,42	p=0,001	p=0,04	p=0,002	p=0,001

mal BMI. The dynamics of average body length is presented in Fig. 1.

Newborns born to obese mothers had statistically significantly higher body length indices than newborns born to mothers with normal BMI (p=0.009). At one month of age, the average body length was almost similar in both groups (p=0.184). However, subsequent decremental check-ups showed that the comparison group had higher body length indices than the controls at 3 months (p <0.001), 6 months (p=0.001), 9 months (p <0.001) and 12 months (p <0.001). This was attributed to higher body length gains at 1–3 and 6–9 months. The data are summarized in Table 1.

The level of physical development in children during the first year of life was assessed by comparing body length with WHO age-specific standards (Child Growth Standards, 2006). The Z-score for body length was calculated for each child. Depending on the individual Z-score value, children were divided into the following groups:

- average physical development (APD) — Z-score between +1 and –1;
- below average physical development (BAPD) — Z-score in the range from 1.1 to 2.0;
- low physical development (LPD) — Z-score ≤–2.1;
- above average physical development (AAPD) — Z-score in the range from +1.1 to +2;
- high physical development (HPD) — Z-score ≥+2.
- The distribution of children in both groups by level of physical development is shown in Fig. 2.

Average physical development in newborns in both groups was recorded with the same frequency (29.6 and 19.4%, p=0.1). Frequency of other variants of physical development showed

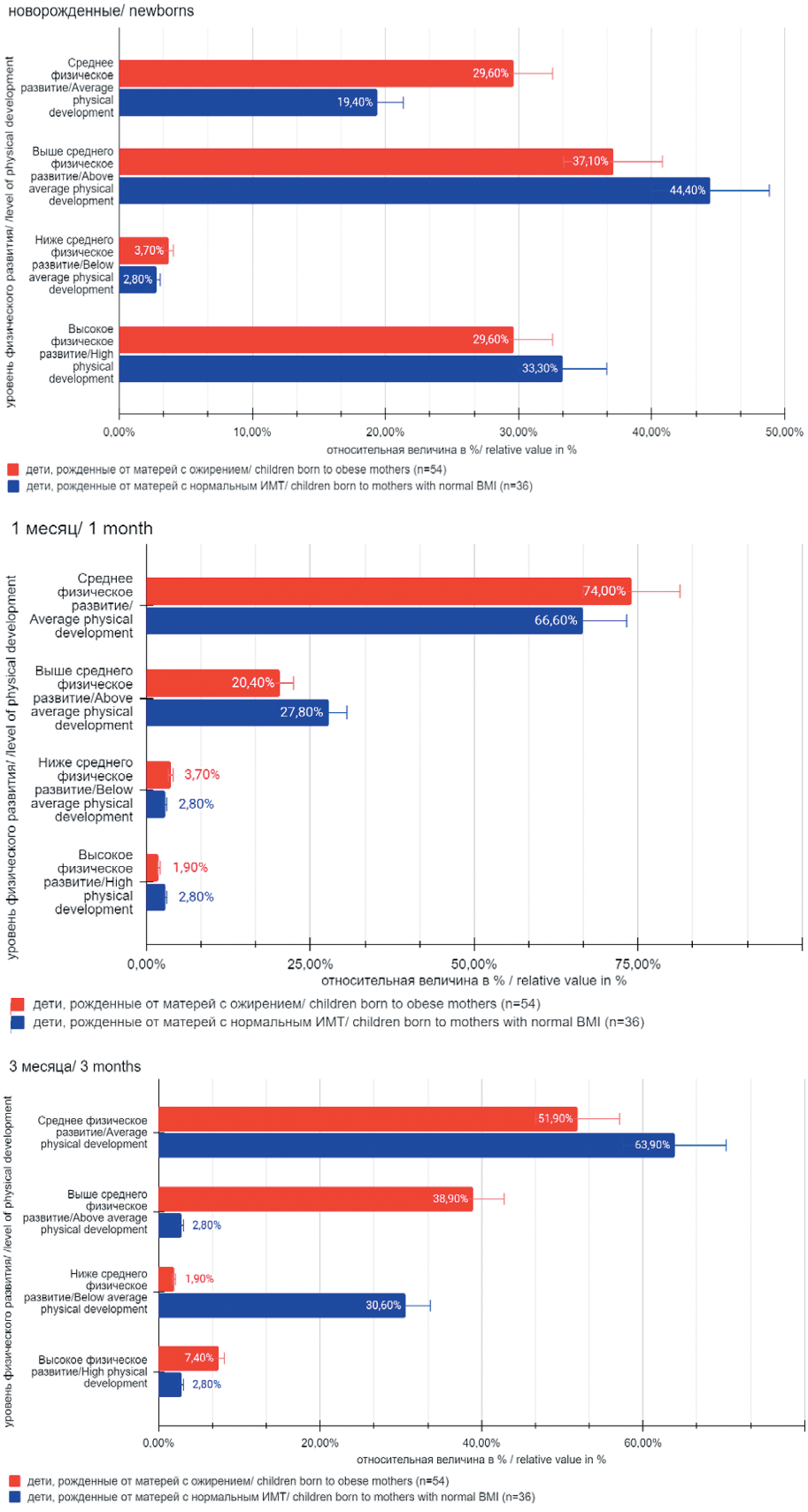

Fig. 2. Distribution of children by level of physical development, in groups of children born to obese mothers and mothers with normal BMI

Рис. 2. Распределение детей по уровню физического развития в группах детей, рожденных от матерей с ожирением и матерей с нормальным ИМТ

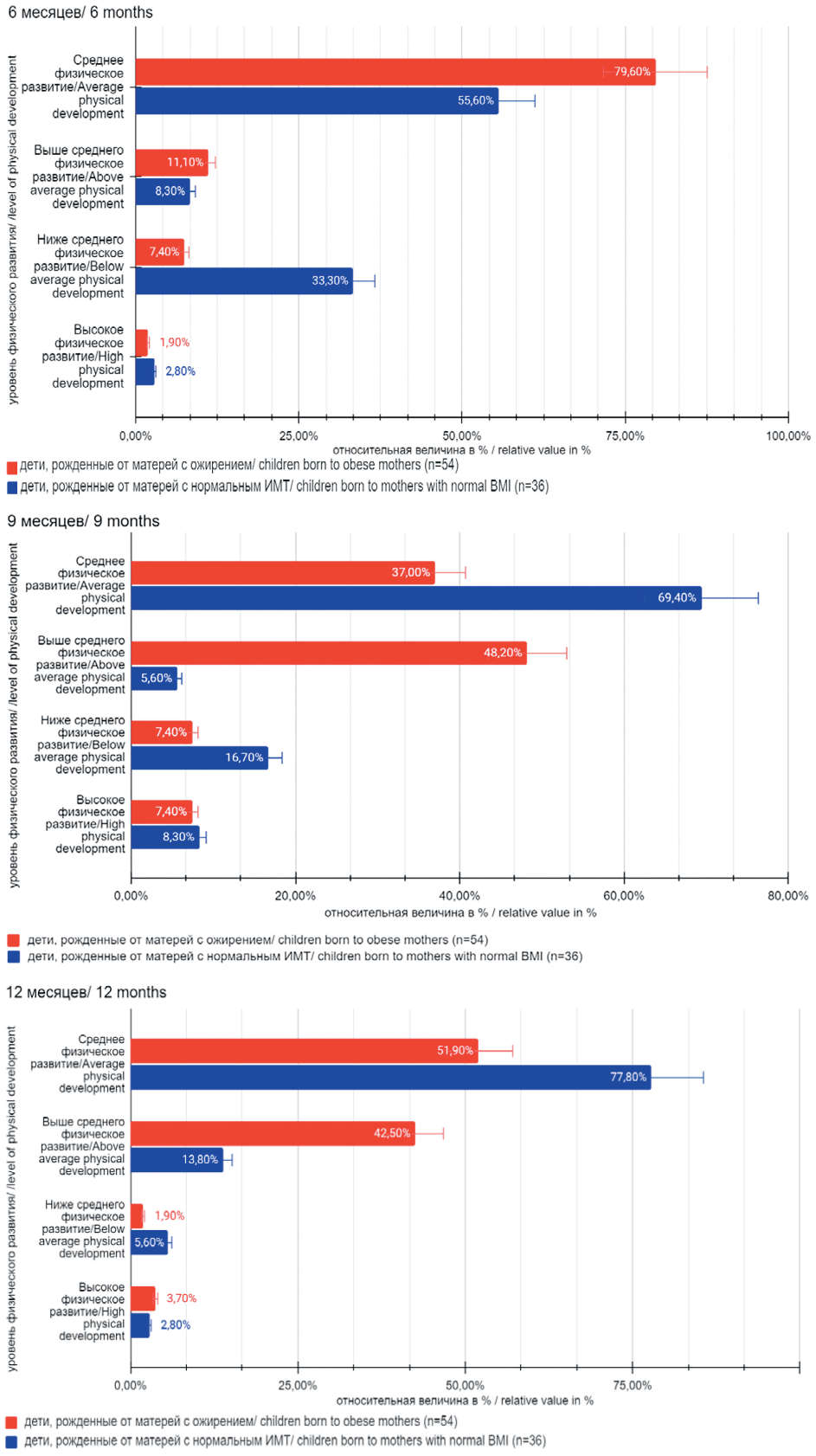

Fig. 2. *Continuation*. Distribution of children by level of physical development, in groups of children born to obese mothers and mothers with normal BMI

Рис. 2. *Продолжение*. Распределение детей по уровню физического развития в группах детей, рожденных от матерей с ожирением и матерей с нормальным ИМТ

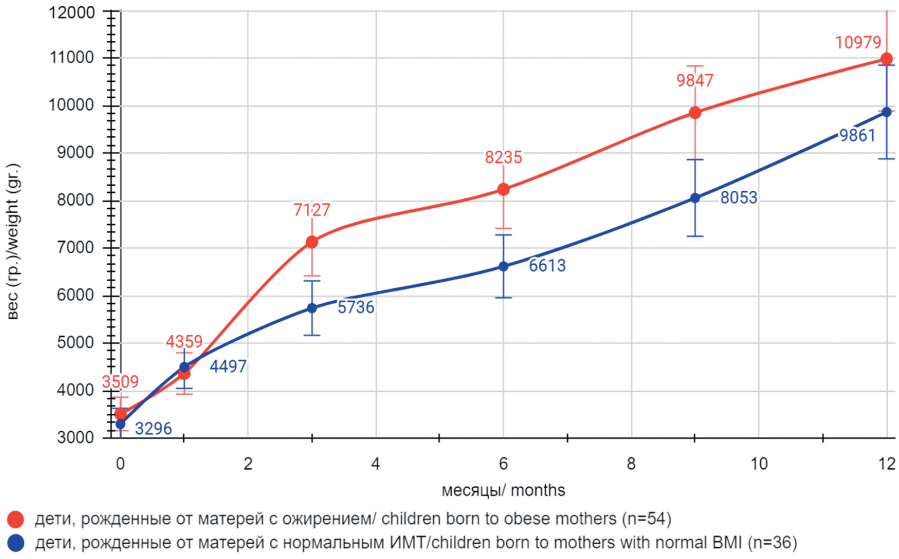

Fig. 3. Dynamics of body weight in children born to obese mothers and children born to mothers with normal BMI

Рис. 3. Динамика массы тела у детей, рожденных от матерей с ожирением, и детей, рожденных от матерей с нормальным ИМТ

no statistically significant difference. However, newborns in Group 1 were more likely to have below average physical development (3.7 and 2.8%) compared to those in Group 2.

At one month of age, all variants of physical development were registered with the same frequency in the studied groups: APD (74.0 and 66.6%, p=0.4), BAPD (3.7 and 2.8%, p=0.3), AAPD (20.4 and 27.8%, p=0.4) and HPD (1.9 and 2.8%, p=0.3).

At 3 months of age, children born to obese mothers were statistically more likely to have AAPD (38.9 and 2.8%, p=0.002) compared to controls. Children born to women with normal BMI were more often diagnosed with average physical development (51.9 and 63.9%, p=0.08) and below average physical development (1.9 and 30.6%, p=0.004). High physical development appeared with equal frequency in the two groups (7.4 and 2.8%, p=0.3).

At 6 months of age, children born to obese women were more likely to have average physical development (79.6 and 55.6%, p=0.04) than the comparison group. AAPD (11.1 and 8.3%, p=0.08) and HPD (1.9 and 2.8%, p=0.2) had no statistically significant differences in both groups. Below average physical development was statistically significantly more common in children born to women with normal BMI (7.4 and 33.3%, p=0.03).

At 9 months, average physical development was more frequently recorded in children born to women with normal BMI (37.0 and 69.4%, p=0.03), while children born to obese women were more frequently diagnosed with AAPD (48.2 and 5.6%, p=0.002). High physical development (7.4 and 8.3%, p=0.1) and below average physical development (7.4 and 16.7%, p=0.4) were diagnosed with equal frequency in both groups.

At 12 months, above average physical development was more often registered in Group 1 (42.5 and 13.8%, p=0.004). Average physical development (51.9 and 77.8%, p=0.04) was statistically significantly more often registered in Group 2. Below average physical development (1.9 and 5.6%, p=0.3) and high physical development (3.7 and 2.8%, p=0.4) had no statistically significant differences in the groups.

The average values of body weight indices in the group of neonates born to obese mothers were also higher than in neonates born to mothers with normal BMI (p=0.004). At the age of one month, body weight indices in both groups had no differences (p=0.150). However, starting from 3 months of life, the body weight indices of children in the first group were higher than in the second group (p <0.001). The data are presented in Fig. 3.

Children born to obese women had more significant weight gain in the period from 1 to 9 months. However, in the period from 9 to 12 months, statistically significant weight gain was higher in children from women with normal BMI. The data are summarized in Table 2.

Absolute body weight values were assessed according to the individualized Z-score. Individual Z-score weight values between +1 and –1 were taken as average body weight values. Undernu-

Table 2. Rates of weight gain (g) in children born to obese mothers and mothers with normal BMI during the observation period

Таблица 2. Темпы прибавки массы тела (г) у детей, рожденных от матерей с ожирением и матерей с нормальным ИМТ, за период наблюдения

Прибавки массы тела в группах (г) / Body weight gain in groups (g)	Период, месяцы / Period, months				
	0–1	1–3	3–6	6–9	9–12
Дети от матерей с ожирением / Children of obese mothers	850±55	2768±16	1108±12	1612±40	1132±135
Дети от матерей с нормальным ИМТ / Children from mothers with normal BMI	1097±102	1239±86	877±43	1440±151	1808±34
Примечание / Note	p=0,2	p=0,001	p=0,04	p=0,06	p=0,02

trition (UN) was diagnosed when body weight Z-score was between –1.1 and –2. Malnutrition (MN) was diagnosed with body weight Z-score ≤–2.1. A child was considered to be overweight (OW) if body weight Z-score was ≥+1.1. Children with Me ≥+2SD were analyzed separately. The distribution of body weight values in both groups is shown in Fig. 4.

The predominant number of newborns had average absolute body weight values by the moment of birth (55.6% in Group 1, and 55.6% in Group 2) p=0.5). Underweight (5.6 and 8.3%, p=0.2) and overweight (3.7 and 8.3%, p=0.1) had no statistically significant differences in both groups at birth . This trend was maintained until 3 months of age.

At 3 months, average body weight values were more often registered in the group of children born to women with stable normal BMI (44.4 and 77.8%, p=0.02), while children born to obese mothers were statistically significantly more often diagnosed as overweight (40.8 and 5.6%, p=0.02). Children in this group were also more likely to have body weight values ≥+2SD (7.4 and 2.8%, p=0.04). Undernutrition (3.7 and 11.1%, p=0.04) was more frequently recorded in children from women with normal BMI. Malnutrition was equally registered in both groups (p=0.1).

At 6 months, average body mass indices were more frequently registered in Group 1 (70.4 and 44.4%, p=0.02). Overweight was also more frequently diagnosed in children of the 1st group (25.9 and 11.2%, p=0.04), while undernutrition (0.0 and 22.2%, p=0.02) and malnutrition (0.0 and 16.7%, p=0.02) were statistically more frequently registered in the 2nd group.

At 9 months, average body weight indices had no statistically significant differences in both groups (37.0 and 50.0%, p=0.1). Undernutrition (1.9 and 22.2%, p=0.03) was more frequently recorded in the group of children from women with normal BMI, and overweight was more frequently diagnosed in the group of children from obese women (48.1 and 11.2%, p=0.02).

At 12 months, overweight was more frequently diagnosed in Group 1 (50.0 and 25.0%, p=0.01). Children in Group 1 were statistically more likely to have body mass indexes above ≥+2SD (14.8 and 8.3%, p=0.04). Undernutrition was more frequently recorded in Group 2 (1.9 and 11.2%, p=0.03). Average body weight (29.6 and 47.2%, p=0.1) and malnutrition (3.7 and 8.3%, p=0.4) were equally registered in both groups.

The harmony of physical development was assessed by Kettle's mass and height index 2. Its value was determined by dividing body weight (kg) by the square of body length (m2). The following variants of physical development were distinguished depending on BMI: harmonious physical development (HFD), Z-score +1 to –1; disharmonious physical development due to body mass deficiency (BMD), Z-score –1.1 to –2; malnutrition (MN), Z-score BMI ≤–2.1; overweight (OW), Z-score +1.1 to +2. Children with Me ≥+2SD were analyzed separately. A comparative analysis of distribution in both groups according to harmony of body length/weight ratio is presented in Fig. 5.

At birth, harmonious physical development was registered in the predominant majority of newborns in both groups and had no statistically significant differences (74.1 and 61.1%, p=0.2). Disharmonious physical development due to overweight (3.7 and 8.3%, p=0.3), underweight (14.8 and 19.5%, p=0.09) and malnutrition (3.7 and 8.3%, p=0.3) was diagnosed with equal frequency in both groups.

During the first month, harmonious physical development was also observed in the majority of infants in both groups (46.3% and 55.5%, p=0.3). However, children born to obese mothers were

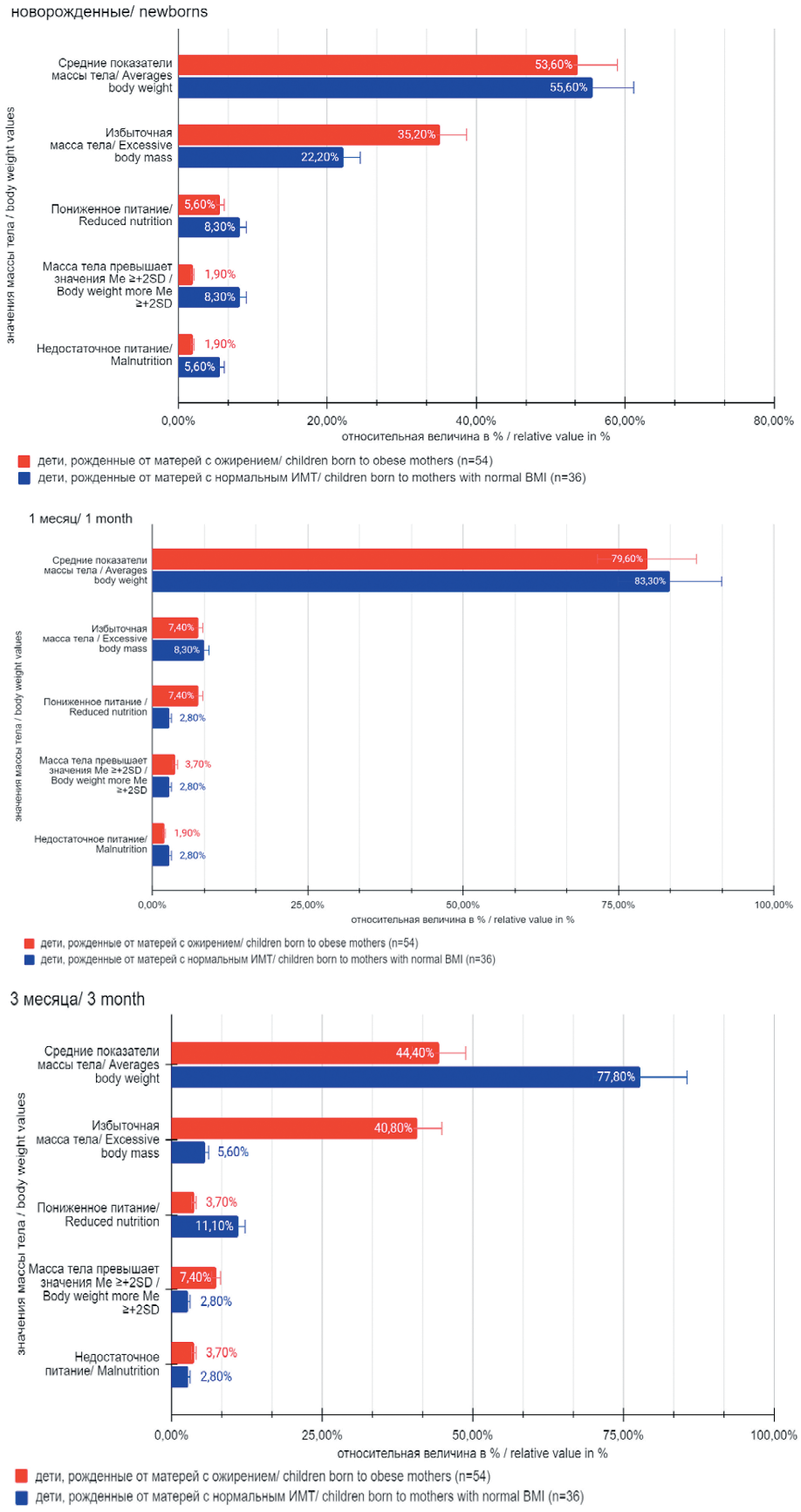

Fig. 4. Distribution of children by body weight, in groups of children from obese women and women with normal BMI

Рис. 4. Распределение детей по массе тела в группах детей от женщин с ожирением и женщин с нормальным ИМТ

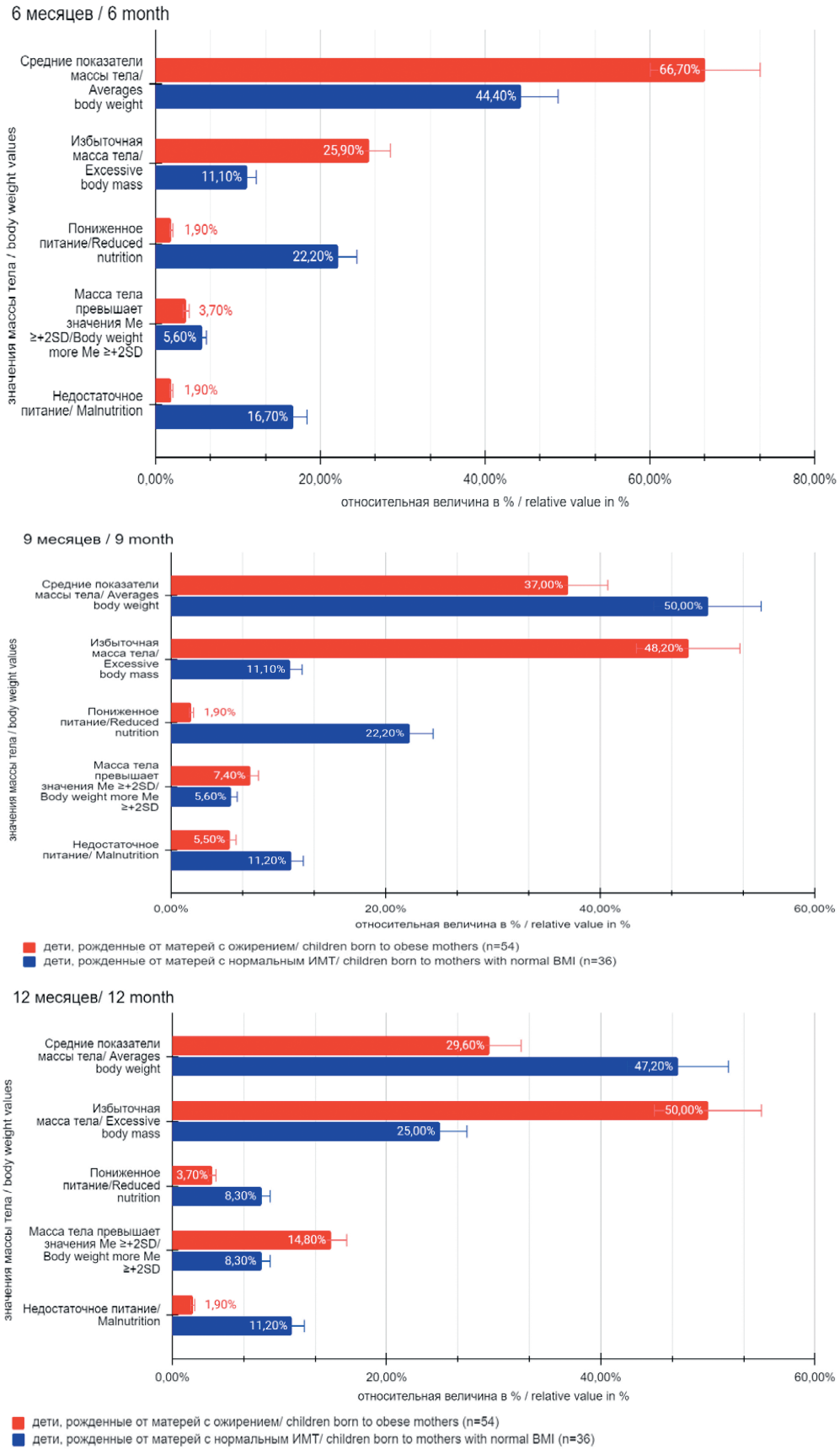

Fig. 4. *Continuation*. Distribution of children by body weight, in groups of children from obese women and women with normal BMI

Рис. 4. *Продолжение*. Распределение детей по массе тела в группах детей от женщин с ожирением и женщин с нормальным ИМТ

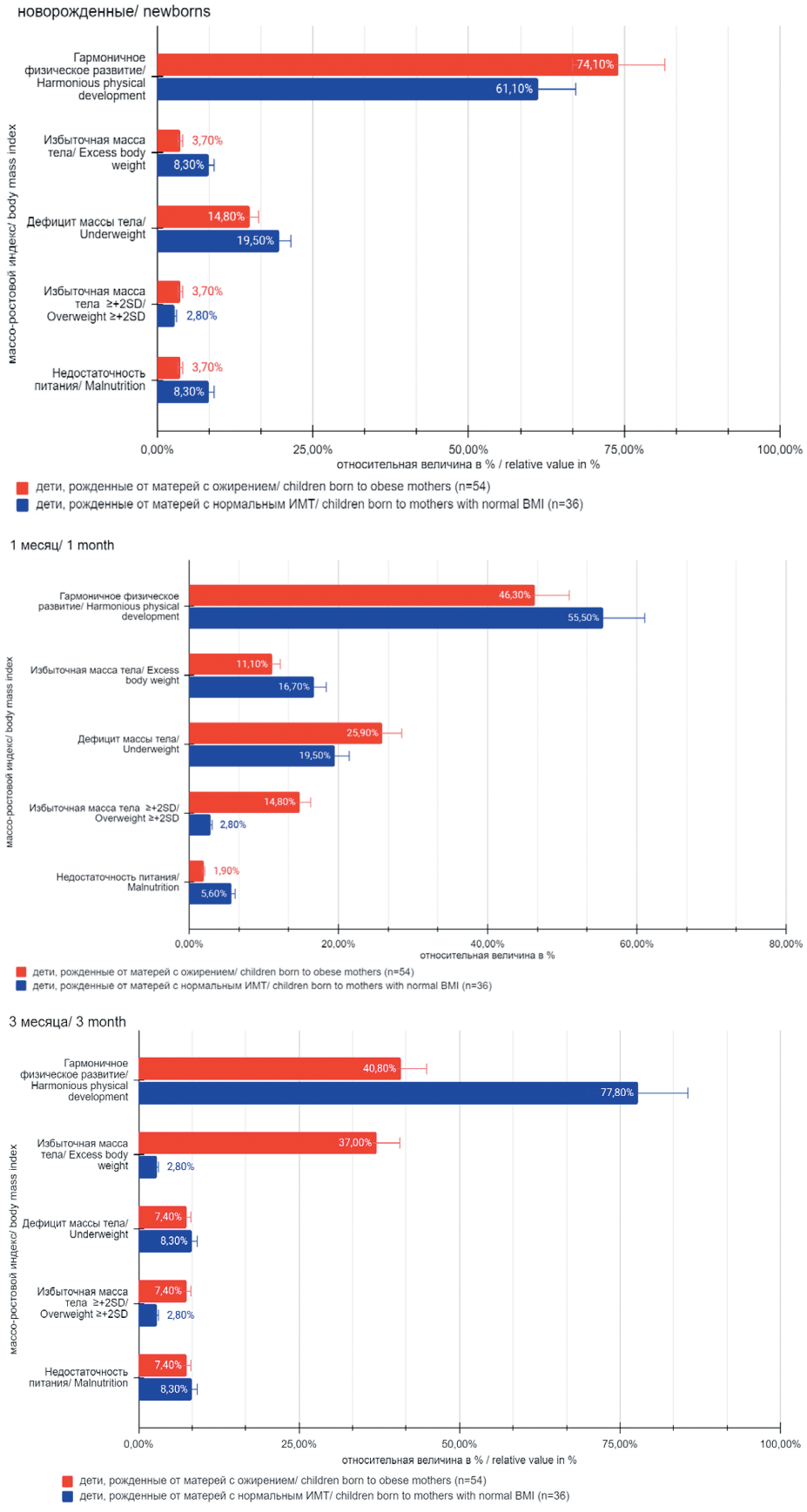

Fig. 5. Distribution of children by body mass index (BMI) in groups of children from obese mothers and mothers with normal BMI

Рис. 5. Распределение детей по массо-ростовому индексу (ИМТ) в группах детей от матерей с ожирением и матерей с нормальным ИМТ

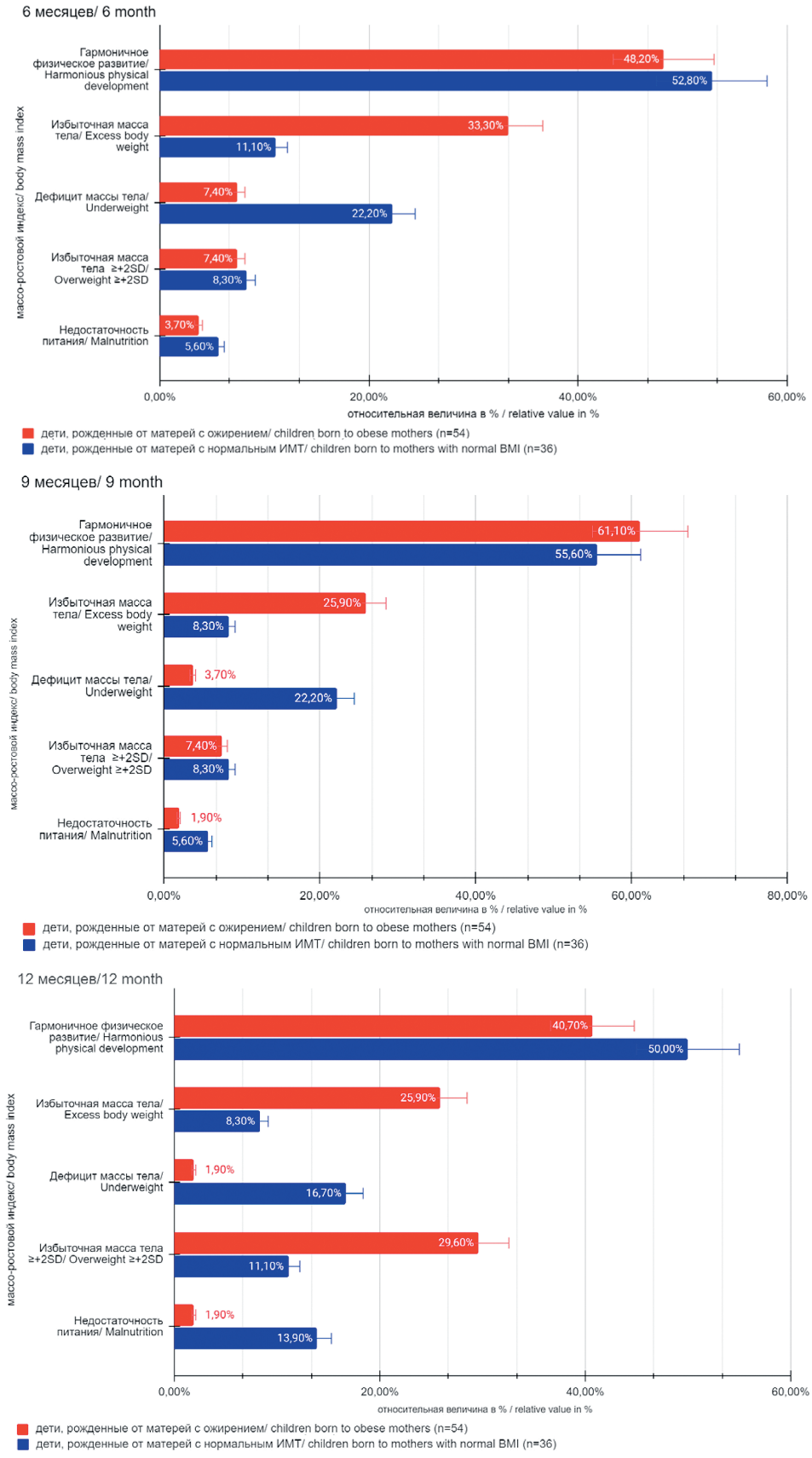

Fig. 5. *Continuation*. Distribution of children by body mass index (BMI) in groups of children from obese mothers and mothers with normal BMI

Рис. 5. *Продолжение*. Распределение детей по массо-ростовому индексу (ИМТ) в группах детей от матерей с ожирением и матерей с нормальным ИМТ

statistically more often diagnosed with excessive body weight exceeding Me ≥+2SD (14.8 and 2.8%, p=0.04). The frequency of disharmonious physical development due to body weight deficiency (25.9 and 19.5%, p=0.1) and malnutrition (0.0 and 5.6%, p=0.3) had no statistically significant differences in the studied groups.

At 3 months, children in Group 2 were statistically significantly more likely to have harmonious physical development (40.8 and 77.8%, p=0.03), while children in Group 1 were statistically more likely to demonstrate disharmonious physical development due to excess body weight (37.0 and 2.8%, p=0.02). However, excessive body weight which exceeded Me ≥+2SD occurred equally often in both groups (7.4 and 2.8%, p=0.3). Disharmonious physical development due to body weight deficiency (7.4 and 22.2%, p=0.04) and malnutrition (7.4 and 8.3%, p=0.1) was recorded with equal frequency in both groups.

At 6 months, harmonious physical development prevailed in all groups (48.2 and 52.8%, p=0.4). Disharmonious physical development due to excessive body weight (33.3 and 11.1%, p=0.03) was registered more often in children born to obese women. However, there were no statistically significant differences in the disharmonious physical development due to BMI exceeding Me ≥+2SD (7.4 and 8.3%, p=0.1). Children born to women with normal BMI were more frequently diagnosed with disharmonious physical development due to weight deficit (7.4 and 22.2%, p=0.04). Malnutrition (3.7 and 5.6%, p=0.1) was diagnosed with equal frequency in the groups.

At 9 months, the majority of children in both groups had a body weight to body length ratio (BWLR) of 61.1 and 55.6% (p=0.2). Group 1 showed a predominance of disharmonious variants of physical development caused by excessive body weight (25.9 and 8.3%, p=0.04), while controls demonstrated disharmonious physical development due to weight deficit (3.7 and 22.2%, p=0.02). Overweight exceeding Me ≥+2SD (7.4 and 9.3%, p=0.1) and malnutrition (1.9 and 8.3%, p=0.07) occurred with equal frequency in both groups.

At 12 months, harmonious physical development prevailed in both groups as well (40.7 and 50.0%, p=0.2). Children born to obese women more often had disharmonious physical development due to excessive body weight (25.9 and 8.3%, p=0.04), including those exceeding Me ≥+2SD (29.6 and 11.1%, p=0.03). In contrast, children born to women with normal BMI were more often diagnosed with disharmonious physical development due to weight deficit (29.6 and 11.1%, p=0.03). Malnutrition was diagnosed with the same frequency (1.9 and 13.9, p=0.06).

There was also conducted a correlation analysis of the dynamics of body length, body weight and weight-growth index of children depending on the mother's BMI. Correlation analysis revealed a positive correlation of maternal BMI with offspring body weight at birth, length and body weight of children at the age of 3, 6, 9 and 12 months, as well as a positive correlation of maternal BMI with the weight-growth index of children at the age of 6 and 12 months. The data are presented in Table 3.

The obtained results demonstrate that children born to obese mothers have higher integral indices of physical development at birth. It is worth noting that there is a tendency to accelerate the rate of weight and body length gain starting from 3 months of life in Group 1. Thus, this group demonstrates statistically significant differences

Table 3. Correlation of maternal BMI with indicators of physical development in children in both groups

Таблица 3. Корреляция материнского ИМТ с показателями физического развития у детей в обеих группах

Показатель / Index	Новорожденные / Newborns	1 месяц / 1 month	3 месяца / 3 month	6 месяцев / 6 month	9 месяцев / 9 month	12 месяцев / 12 month
Длина тела / length	r=0,043 p=0,799	r=–0,171 p=0,305	r=0,650** p<0,01	r=0,453* p=0,004	r=0,751** p<0,01	r=0,375* p=0,02
Масса тела / Body mass	r=0,772** p <0,01	r=–0,088 p=0,6	r=0,562** p <0,01	r=0,592** p <0,01	r=0,505** p=0,001	r=0,350* p=0,03
Массо-ростовой индекс/ Body mass index	r=0,170 p=0,308	r=-0,153 p=0,361	r=0,285 p=0,083	r=0,537** p=0,001	r=0,039 p=0,817	r=0,456* p=0,02

**Корреляция значима на уровне 0,01 (двухсторонняя) / Correlation is significant at the 0.01 level (2-tailed).

*Корреляция значима на уровне 0,05 (двухсторонняя)/ Correlation is significant at the 0.05 level (2-tailed).

in disharmony of physical development at the age of 12 months, mainly due to excessive body weight.

CONCLUSION

The obtained results of physical development analysis prove the influence of maternal obesity on anthropometric indicators in offspring and indicate the risks of obesity and metabolic syndrome formation at an early age. Children with excess body weight at 12 months are at risk of developing obesity at school age. Childhood obesity is associated with metabolic disorders — diseases of the cardiovascular system, gastrointestinal tract, and musculoskeletal system in adulthood. The topic requires further study to identify possible mechanisms of maternal obesity influence on the physical development and health of offspring as well as to identify simple, accurate markers of metabolic disorders associated with obesity in young children.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

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THE SIGNIFICANCE OF CLINICAL AND LABORATORY SIGNS IN ASSESSING THE EFFECTIVENESS OF NUTRITIONAL SUPPORT FOR CRITICALLY ILL NEWBORNS

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Abstract. ***Introduction.*** The choice of starting nutritional support in newborns depends on the severity of multiple organ failure and the initial metabolic process in the early neonatal period. ***The purpose*** is to study the prognostic value of clinical and laboratory parameters in assessing the metabolic status of newborns in need of nutritional support. ***Materials and methods***. 125 newborns are included in the study. They are divided into 2 groups: 69 children with the somatic disorder symptoms, 55 with surgical pathology. Prognostic assessment of biochemical markers and their relationship with nosological profile and nutritional corrected types is performed using statistical methods of data processing. ***Results and conclusion.*** In patients with somatic disorders cardiorespiratory hypoxia affects the nutritional status in the short term. The tolerance to full enteral nutrition is restored within a week. Surgical trauma is associated with the hypercatabolic syndrome, dysproteinemia and fluctuations in body weight. The prognostic value of death is determined in groups: in the surgical one with C-reactive protein growth (AUC >0,9, p=0,000), the elevated of blood urea nitrogen after surgery (AUC >0,8, p=0,000) and lactate on the 7th day (AUC=0,989, p=0,000); in newborns with the somatic disorder C-reactive protein growth is valuable in ICU admission and glucose concentration is on the 7th day (AUC=0,88 and AUC=0,94, p=0,000 respectively). For nutritional support, the values of C-reactive protein are relevant in the somatic group. There are actual levels of glucose, blood urea nitrogen, albumin on the first postoperative day. The duration of parenteral nutrition is significantly affected by surgical treatment and albumin transfusion (p=0.000), η^2=26.4% (ANOVA method). In the choice of nutritional support the personalized approach is important to determine metabolic status.

Keywords*: newborns, metabolic status, parenteral nutrition, intensive care*

ЗНАЧИМОСТЬ КЛИНИКО-ЛАБОРАТОРНЫХ ПРИЗНАКОВ В ОЦЕНКЕ ЭФФЕКТИВНОСТИ НУТРИТИВНОЙ ПОДДЕРЖКИ У НОВОРОЖДЕННЫХ В КРИТИЧЕСКОМ СОСТОЯНИИ

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Резюме. ***Введение.*** Выбор нутритивной поддержки и ее начало у новорожденных зависит от тяжести полиорганной недостаточности, характера патологии, исходного метаболического статуса**.** ***Цель исследования*** — изучение прогностической ценности клинико-лабораторных показателей в оценке метаболического статуса у новорожденных, нуждающихся в нутритивной поддержке. ***Материалы и методы.*** Исследование проведено у 125 новорожденных, распределенных на 2 группы: соматическая — 69 детей, хирургическая — 56 детей. Прогностическая оценка биохимических маркеров и их взаимосвязь с патологией и видами нутритивной коррекции выполнена статистическими методами обработки данных. ***Результаты и выводы.*** У соматических пациентов гипоксия вследствие кардиореспираторной депрессии влияет на нутритивный статус краткосрочно с восстановлением толерантности к полному энтеральному питанию в течение недели. Операционная травма сопряжена с развитием гиперкатаболического синдрома, проявляющегося тяжелой диспротеинемией колебаниями массы тела. Прогностическую ценность неблагоприятного исхода определили: в хирургической группе рост С-реактивного белка AUC >0,9, p=0,000, уровень азотемии после операции AUC >0,8, p=0,000, лактата на 7-е сутки AUC=0,989, p=0,000; в соматической группе — С-реактивный белок при поступлении и концентрации глюкозы на 7-е сутки (соответственно, AUC=0,88 и AUC=0,94, p=0,000). Для проведения нутритивной поддержки актуальны значения С-реактивного белка в соматической группе, в хирургической — уровни глюкозы, мочевины, альбумина в 1-е сутки послеоперационного периода. На длительность парентерального питания значимо влияют проведенное хирургическое лечение и трансфузия альбумина (p=0,000), η^2=26,4 % (метод ANOVA). Персонифицированный подход определения метаболического статуса остается актуальным в выборе нутритивной поддержки.

Ключевые слова*: новорожденные, метаболический статус, парентеральное питание, интенсивная терапия*

INTRODUCTION

Counteracting critical conditions requires significant metabolic demands from patients, especially in the neonatal period [1, 2]. Nutritional deficiency significantly hinders the metabolic effects of nutrients, moreover, it is a universal component of multiorgan failure syndrome and requires comprehensive clinical and laboratory monitoring [2, 3]. The developed clinical protocols for parenteral and enteral nutrition in newborns do not take into account the peculiarities of dysmetabolism in newborns in critical condition associated with gastrointestinal insufficiency in the postoperative period, the presence of congenital malformations of the gastrointestinal tract and intrauterine developmental delay [3–5]. According to studies [6, 7], more than 70% of neonates operated during the neonatal period had a body weight deficit below the 50th centile and required nutritional correction. The need for a better understanding of the changes in the metabolic status of neonates in critical condition determined the relevance of the study.

AIM

To study a prognostic value of clinical and laboratory parameters in the assessment of metabolic status in neonates requiring nutritional support.

MATERIALS AND METHODS

The observational study was conducted at the paediatric intensive care unit (ICU) of the State Novosibirsk Regional Clinical Hospital approved by the Local Ethics Committee of the State Novosibirsk Regional Clinical Hospital (protocol No. 1 of 09.03.2021). The total study sample consisted of 125 newborns hospitalized from 2020 to 2022. Gender distribution: boys — 72 (58%), girls — 53 (42%). Newborns were divided into two groups depending on the presence or absence of surgical pathology requiring surgical treatment for urgent and emergency indications: somatic — 69 (group 1), surgical — 56 (group 2). 50 patients (40%) had gestational age less than 37 weeks, 18 patients (14%) had fetal growth restriction (FGR). There were 7 (5.6%) deaths: 4 in the somatic group and 3 in the surgical group.

Inclusion criteria: Group 2 required surgical treatment of intestinal pathology. All participants were included in the study in case of the neonatal period (up to 28 days of life at admission), absence of cardiovascular insufficiency with shock development, indications for long-term parenteral nutrition. Nosological characteristics of the groups: Somatic group- presence of intrauterine infection (pneumonia, enterocolitis stage I–II) — 15 (22%), congenital heart defect — 13 (19%), early neonatal sepsis — 8 (12%), respiratory distress

syndrome of prematurity — 23 (33%), other — 8 (12%); Surgical group — oesophageal atresia — 14 (36%), high intestinal obstruction — 5 (9%), low intestinal obstruction — 15 (27%), gastroschisis — 2 (3.6%), diaphragmatic hernia — 4 (7%), necrotising enterocolitis (NEC) grade III — 5 (9%), other — 9 (16%). Complications in the somatic group: infectious ones — 26 (38%), haemorrhagic — 3 (4%), in the surgical group: infectious — 21 (37.5%), haemorrhagic — 4 (7.1%).

There were no significant intergroup differences in mortality and number of complications. Intensive therapy was performed according to the generally accepted algorithm: respiratory therapy to achieve target ventilation/oxygenation parameters; hemodynamic therapy: to ensure the volume of daily hydration according to physiological needs with recalculation per day of life (for preterm neonates — from 40 ml/kg to reach 130 ml/kg, less than 37 weeks of gestation — from 60 to 140 ml/kg). Isotonic saline solutions, components of parenteral nutrition, and dilutions were included in the calculation. When enteral nutrition (EN) had been tolerated, the volume of intravenous infusion was reduced. The algorithm and composition of parenteral nutrition (PN) were performed according to modern protocols [1, 5]. PN was performed in 101 neonates (81%), albumin transfusion — in 60 patients (48%). The substrate-energy composition of nutritional support is presented in Table 1. The need for parenteral nutrition in the surgical group was 211 hours (138; 301) and 118 hours (89; 160) in the somatic group, p=0.000. The somatic group achieved adequate volume of enteral nutrition earlier at all stages (p <0.05).

The studied parameters were recorded over 3 stages: for surgical patients: stage 1 — the first day after surgical treatment (when administered to ICU), 2 — the third day, 3 — the sixth-seventh day. The same time stages were used for somatic patients according to the time of stay in ICU. The study included general clinical parameters (leukocyte (Le), haemoglobin (Hb), haematocrit (Ht) levels), biochemical monitoring (ionised calcium (Ca^{2+}), potassium (K), C-reactive protein (C-RP), total protein (Prot), lactate (Lac), glucose (Glu), albumin (Alb.), urea (Ur), creatinine (Cr), anthropometric data.

Statistical processing of the material was performed using IBM SPSS Statistics 20 program, USA. Taking into account the non-normal nature of data distribution (Kolmogorov–Smirnov criterion), mathematical processing was carried out using nonparametric statistics methods. The results are presented in tables and graphs in the form of median with values of lower and upper quartile (Q25; Q75). Two independent signs were compared by the Mann–Whitney test, dependent pairs of signs — by the Wilcoxon test, dependent 3 signs and more — by the Friedman test, correlation analysis — by the Spearman rank test. Predictive analytics was performed by ROC-analysis methods (calculation of area under the ROC-curve (AUC), overall model characterization (SE standard error, CI 95%: confidence interval) and decision tree construction (CHAID method). The influence of factors was assessed by multivariate analysis of variance (ANOVA), η^2%. The null hypothesis was rejected at p <0.05.

RESULTS AND DISCUSSION

The neonates were compared in terms of the fetal growth restriction (FGR) incidence (Table 2). Odds Ratio (OR) = 1 (95% CI 0.4–2.7), preterm infants were 3.5 times more common in the somatic group: p=0.001, OR 3.5 (95% CI 1.5–4.7).

Table 1. Substrate provision and enteral nutritive initiation in groups at stages

Таблица 1. Субстратное обеспечение и начало энтерального питания в группах на этапах

Этап / Stage	Показатель / Indicator				
	№ гр. / gr. №	белок, г/кг/сутки / protein, g/kg/day	углеводы, г/кг/сутки / carbohydrates, g/kg/day	энергия, ккал/кг/сутки / energy, kcal/kg/day	ЭП, % / EN, %
1	1	1,5 (1; 2)	6,3 (4,7; 8,6)	38 (36; 48)	0
	2	1,25 (0,5; 2)	6,2 (4; 8,4)	40 (22; 50)	0 (0; 20)
2	1	2,8 (2; 3)	11,3 (8; 13)	68 (49; 74)	0 (0; 20)
	2	2 (1,6; 3)	9,2 (7; 12,4)	60 (40; 72)	20 (0; 50)
3	1	2,5 (1,3; 3)	10 (5,5; 13,3)	65 (30; 75)	30 (10; 70)
	2	2 (1; 2,5)	9,3 (6,3; 11,6)	60 (41; 71)	60 (30; 80)

Table 2. Anthropometric characteristics of groups

Таблица 2. Антропометрические характеристика групп

Показатель / Indicator	Группа 1 / Group 1 (n=69)	Группа 2 / Group 2 (n=56)	Критерий Манна–Уитни / Mann–Whitney test
Масса тела, г / Body weight, g	2690 (2440; 3180)	3120 (2455; 3470)	p=0,105
Возраст, дни / Age, days	1 (1; 8)	2 (1; 6)	p=0,664
Апгар, балл / Apgar, score	7/7 (6/7; 7/8)	7/8 (7/8; 8/9)	p=0,002
Срок гестации, недели / Gestation period, weeks	35 (33; 38)	38 (37; 39)	p=0,021

Table 3. General clinical and carbohydrate status in two groups at stages

Таблица 3. Общеклинический и углеводный статус в двух группах на этапах

Этап / Stage	Показатель / Indicator					
	№ гр. / gr. №	Le, 10^9/л / Le, 10^9/l	Hb, г/л / Hb, g/l	Ht, % / Ht, %	Lac, ммоль/л Lac, mmol/l	Glu, ммоль/л / Glu, mmol/l
1	1	13 (11; 18)	147 (128; 170)	44 (40; 52)	*2,2(1,6; 4,4)*	3,8 (3; 4,6)
	2	15 (12; 17)	155 (142; 175)	47 (41; 51)	*1,6(1,3; 2,3)**	4 (3,5; 4,7)
2	1	12 (9; 15)	150 (135; 187)	43 (39; 55)	1,5 (1,2; 2)	4,7 (3,9; 5,4)
	2	13 (10; 19)	148 (130; 171)	45 (38; 49)	1,5 (1,2; 1,9)	4,3 (3,7; 5,1)
3	1	10 (9; 14)	142 (125; 167)	45 (38; 52)	1,8 (1,5; 2,1)	4,7 (4,4; 5)
	2	13 (9; 19)	147 (127; 154)	42 (37; 46)	1,5 (1,2; 1,8)	4,5 (4; 4,9)

* Значимость критерия Манна–Уитни p=0,021.

* Significance of the Mann–Whitney test p=0.021.

The dynamics study of body weight is presented in Figure 1. A significant loss of the parameter was detected in newborns in the postoperative period (Friedman's criterion χ^2=8.11, p=0.04) while the parameter was stable in the somatic group (a trend was detected between the 2nd and 3rd stages, not reaching the accepted level of significance; Wilcoxon's criterion, p=0.065).

When comparing the results of general clinical and biochemical analyses in the groups at stages, the results are generally comparable (Tables 3, 4). Differences in lactate and creatinine concentrations were noted on arrival; multidirectional dynamics in azotaemia remained by the end of the week.

Correlation analysis of different markers have been performed in groups according to Apgar score. It revealed the fact that there is a direct significant association between creatinine at all stages with Apgar score (ρ=0.7, p=0.000; ρ=0.67, p=0.000; ρ=0.54, p=0.000, respectively) and lactate level at admission (ρ=0.72, p=0.000) in the somatic group. The surgical group showed a direct

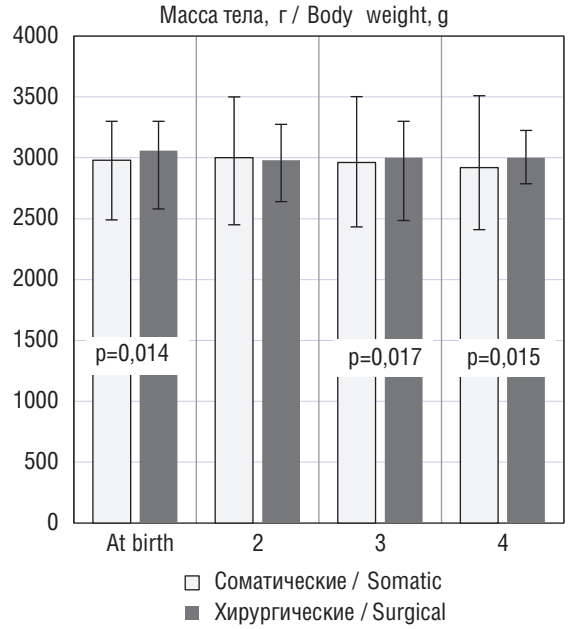

Fig. 1. Dynamics of body weight in groups at the study stages. The Mann–Whitney's test significance

Рис. 1. Динамика массы тела в группах на этапах исследования. Указана значимость критерия Манна–Уитни

Table 4. Biochemical parameters in groups at stages

Таблица 4. Биохимические параметры в группах на этапах

Этап / Stage	Показатель / Indicator							
	№ гр. / gr. №	Ca^2+, ммоль/л / Ca^2+, mmol/l	K+, ммоль/л / K+, mmol/l	C-RP, мг/л / C-RP, mg/l	Prot., г/л / Prot., g/l	Alb., г/л / Alb., g/l	Ur, ммоль/л / Ur, mmol/l	Cr, мкмоль/л / Cr, μmol/l
1	1	1 (0,9; 1,3)	4 (3,8; 4,6)	2 (0,5; 13)	44 (41; 48)	31 (28; 32)	5 (3,4; 8,3)	77 (67; 97)
	2	1 (0,9; 1,2)	4,1 (3,8; 4,8)	6 (1,5; 20)	44 (40; 48)	30 (28; 32)	5,3(3,7; 6,2)	73 (58; 82)*
2	1	1,1 (0,9; 1,3)	4,2 (3,9; 4,5)	2 (1; 7)	45 (42; 47)	31 (29; 32)	6,1 (4,6; 9)	68 (64; 84)
	2	1,2 (1,1; 1,4)	4,4 (3,9; 4,7)	10 (4; 21)	47 (43; 50)	31 (28; 35)	6 (4,8; 9)	59 (52; 78)*
3	1	1,3 (1,1; 1,4)	4,5 (4,1; 4,6)	2 (1,5; 4)	46 (44; 49)	31 (30; 33)	5,2 (4,1; 7,5)	57 (51; 66)
	2	1,3 (1,2; 1,4)	4,5 (4,2; 4,7)	5 (3; 9)	48 (44; 51)	33 (30; 36)	6,9 (5,3; 8,1)*	54 (48; 67)*

* Значимость критерия Манна–Уитни Ur_3 p=0,016, Cr_1 p=0,008; Cr_2 p=0,005, Cr_3 p=0,03.

* Significance of the Mann–Whitney test Ur3 p=0.016, Cr1 p=0.008; Cr2 p=0.005, Cr3 p=0.03.

Table 5. ROC-analysis of indicators in groups at stages (prediction of death)

Таблица 5. ROC-анализ показателей в группах на этапах (прогнозирование летального исхода)

Этап/ Stage	Показатель / Indicator	№ гр. / gr. №	AUC	SE	p	95% ДИ	
	Возраст, дни / Age, days	1	0,814	0,083	0,000	0,651	0,978
		2	0,675	0,075	0,020	0,528	0,822
1	C-RP, мг/л / C-RP, mg/l	1	0,879	0,076	0,000	0,730	0,99
		2	0,917	0,044	0,000	0,831	0,99
3	C-RP, мг/л / C-RP, mg/l	1	0,686	0,098	0,058	0,494	0,878
		2	0,983	0,013	0,000	0,97	0,992
1	Ur, ммоль/л / Ur, mmol/l	1	0,979	0,022	0,000	0,936	0,993
		2	0,883	0,064	0,000	0,757	0,99
1	Cr, мкмоль/л / Cr, μmol/l	1	0,686	0,090	0,039	0,509	0,862
		2	0,803	0,092	0,002	0,610	0,973
3	Glu, ммоль/л / Glu, mmol/l	1	0,943	0,039	0,000	0,866	0,99
		1	0,663	0,088	0,059	0,499	0,838
3	Lac, ммоль/л / Lac, mmol/l	1	0,393	0,095	0,261	0,206	0,580
		2	0,989	0,012	0,000	0,966	0,992

Table 6. ROC-analysis of indicators in groups (prediction of the parenteral nutrition initiate)

Таблица 6. ROC-анализ показателей в группах (прогнозирование начала парентерального питания)

Этап / Stage	Показатель / Indicator	№ гр. / gr. №	AUC	SE	p	95% ДИ	
1	C-RP, мг/л / C-RP, mg/l	1	0,413	0,096	0,362	0,225	0,600
		2	0,898	0,076	0,000	0,749	0,986
2	Alb., г/л / Alb., g/l	1	0,487	0,086	0,878	0,319	0,655
		2	0,819	0,074	0,000	0,673	0,964
1	Ur, ммоль/л / Ur, mmol/l	1	0,499	0,083	0,993	0,337	0,661
		2	0,902	0,070	0,000	0,796	0,993

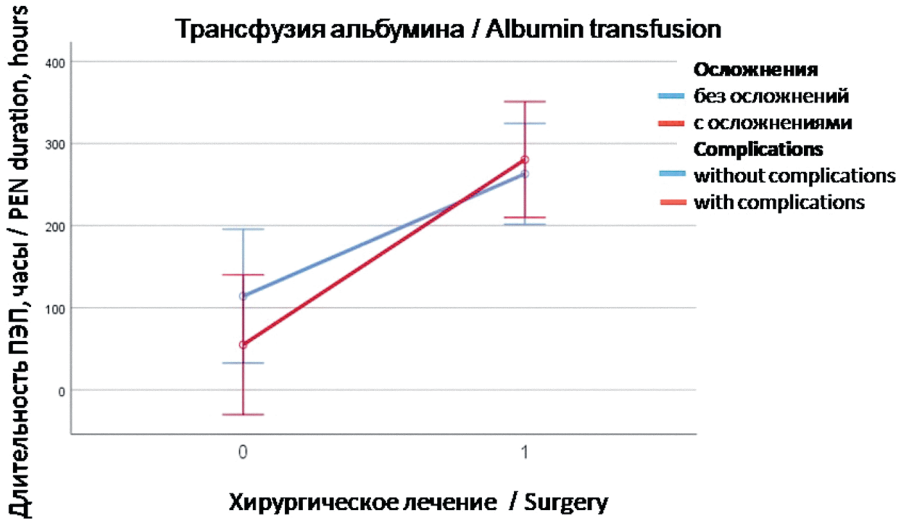

Fig. 2. Interaction of factors (albumin transfusion and complications) and their influence on the duration of parenteral nutrition in groups

Рис. 2. Взаимодействие факторов (трансфузия альбумина и осложнений) и их влияние на длительность парентерального питания в группах

correlation only between urea and creatinine at stage 3 (ρ=0.537, p=0.000).

Prediction of outcome (fatal outcome) and the need for parenteral nutrition was performed by ROC analysis. The ignificant AUC is ≥0.8. Prognostic markers of target variables are presented (Table 5).

The predictive indicators of lethal outcome in the surgical group were C-reactive protein concentrations over 93 mg/l (Se 89%, Sp 85%) in the first three days and lactate concentrations over 5 mmol/l on the 7th day (Se 91%, Sp 83%). Neonates with somatic pathology showed validity of urea concentration on admission greater than 9.4 mmol/l (Se 87%, Sp 82%) and glycaemia less than 3.1 mmol/l (Se 84%, Sp 89%) on the 7th day.

Parenteral nutritional support was initiated in neonates after surgical treatment with C-reactive protein concentrations less than 33 mg/L (Se 83%, Sp 87%) and urea levels less than 4.7 mmol/L (Se 84%, Sp 90%). Albuminemia of more than 24 g/l (Se 86%, Sp 81%) determined tolerance to substrate load on the 3rd day in the somatic group (Table 6). ROC analysis was not informative for predicting complications (factor sign 0/1). The method of multifactorial analysis of variance ANOVA revealed isolated and bifactorial influence of albumin transfusion after surgical treatment of complications during parenteral nutrition (Fig. 2). Both surgical treatment and the need for albumin transfusion appeared to have a statistically significant influence on the duration of PN (p=0.006 and p=0.047 respectively). The correlation of these factors between each other was statistically significant (p=0.000) and had a maximum contribution to the variance of η^2=26.4%.

Taking into account the comparability of the groups in terms of outcome category (χ^2=0.011, p=0.09) and the majority of metabolic indices at the stages, the decision tree method was used to create a prognostic model of unfavourable outcome (lethal outcome) and to identify significant markers of intensive care for the whole sample. Unfavourable signs were anaemia on admission (haemoglobin less than 149 g/l) and kalaemia less than 3.8 mmol/l on the 7th day (Fig. 3).

The present study revealed the nature of pathology on metabolic status in neonates. The influence of initial hypoxia on cardiorespiratory maladaptation and metabolism has been confirmed in neonates with somatic pathology [8]. However, regression is noted within a week without critical catabolic shifts and no weight loss, despite priority restriction of hydration volumes. The literature confirms [9, 10] that surgical trauma is associated with profound metabolic disorders, the development of hypercatabolic syndrome which manifests in severe dysproteinaemia. The number of albumin transfusions was significantly higher in the surgical group χ^2=13, p=0.000, OR=3.8 (95% CI 1.8–8.2). Hypoalbuminaemia in somatic neonates was associated with pre- and postnatal nutrient deficiency (correlation with hypoglycaemia on admission was found). As for sur-

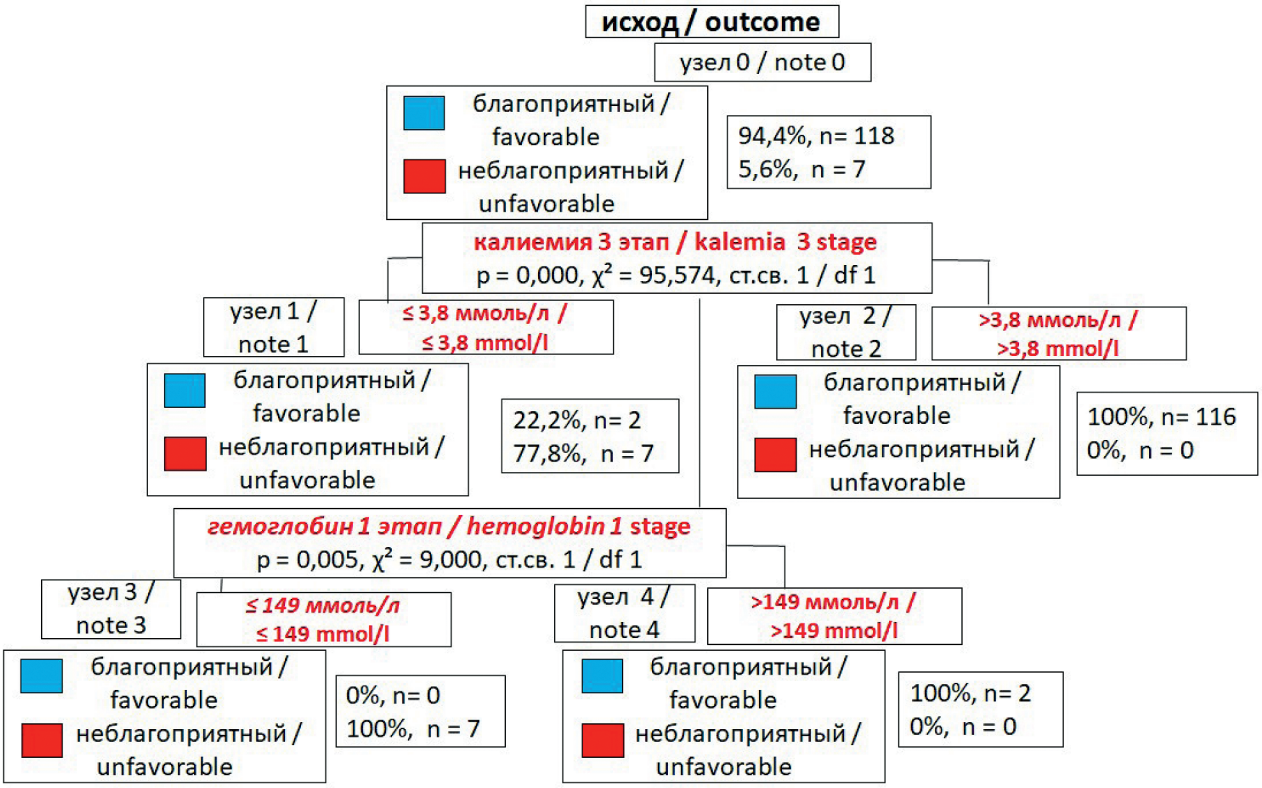

Fig. 3. Decision tree method CHAID (Chi-squared Automatic Interaction Detection)

Рис. 3. Дерево решений, метод CHAID (Chi-squared Automatic Interaction Detection)

gical neonates, it was associated with C-reactive protein concentration, i.e. with intensity of an inflammatory response to surgical aggression. The growth of azotaemia in the postoperative period is associated with the duration of post-stress protein hypercatabolism on the background of replacement therapy. The revealed metabolic shifts in neonates with abdominal surgical pathology confirmed the data presented by the authors [9]. The sergical group was supplied with lower daily amino acid intake during the early postoperative period compared to the somatic group, which was characterised by rapid increase in the volume of enteral nutrition and the amount of substrate-energy support [11, 12]. Studies have confirmed the importance to control the nutrient requirements in neonates after surgical treatment [13, 14]. The opportunity to achieve adequate enteral nutrition determined the stability of the body weight index in this group.

The increase in the enteral nutrition rate was associated with a positive difference in body weight by the 7th day (direct, weak correlation ρ=0.35, p=0.035). The studied groups were compared in relation to the number of unfavourable outcomes (χ^2=0.01, p=0.9, OR=0.9 (95% CI 0.1–4.2) and complications (χ^2=0.09, p=0.8, OR= ,1 (95% CI 0.5–2.3). The structure of complications coincided in the groups. However, an infection component was significant in the somatic pathology during the eraly period, while it apeared in the surgical group remotely. The prognostic unfavourable shifts of indices were revealed: the presence of hemoglobin deficiency on admission (less than 149 g/l) and kalaemia on the 7th day (less than 3.8 mmol/l).

CONCLUSIONS

1. Inflammatory response (C-reactive protein less than 33 mg/L) and decreased azotemia less than 4.7 mmol/L were the criteria for initiation of parenteral nutritional support in neonates in early period after surgical treatment.

2. The rate of initiation of parenteral nutrition in neonates with cardiopulmonary maladaptation was associated with an albuminemia level of more than 24 g/L.

3. C-reactive protein concentration of more than 93 mg/l in the first three days and lactate concentration of more than 5 mmol/l by the end

of the week were determined as prognostic indicators of lethal outcome in newborns after surgical treatment. Azotemia of more than 9.4 mmol/l on admission and glycaemia of less than 3.1 mmol/l were associated with an unfavourable outcome in neonates with somatic pathology. For all neonates, anaemia (haemoglobin less than 149 g/l) and potassium level (less than 3.8 mmol/l) at 7th day were considered as prognostic unfavourable shifts in parameters.

4. A personalized approach to the development and control of metabolic status and nutritional support remains relevant in treating neonates in critical conditions and requires further research.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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THE INFLUENCE OF HELICOBACTER PYLORI ERADICATION THERAPY ON THE COURSE OF GASTROESOPHAGEAL REFLUX DISEASE IN SCHOOL-AGE CHILDREN

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Abstract. ***Introduction.*** Data on the role of *Helicobacter pylori* (Hp) in the development of gastroesophageal reflux disease (GERD) are contradictory; most researchers believe that Hp infection has a protective effect on the incidence of GERD. Ambiguous results have also been obtained regarding the effect of *H. pylori* eradication on the development of GERD, reflux esophagitis and symptoms associated with reflux. Most meta-analyses have found no significant differences in the development of GERD after *H. pylori* eradication between patients with eradication and patients with persistent infection. But a number of studies have reported a significant increase in the risk of GERD after successful eradication therapy. Most studies were conducted on a cohort of adult patients; data on the effect of *H. pylori* on the course of GERD in children are fragmentary. ***Objective.*** To evaluate the effect of eradication therapy on the course of gastroesophageal reflux disease in school-age children. ***Materials and methods***. The study included 55 children from 7 to 17 years 11 months (11.4±2.1 years) with an erosive form of gastroesophageal reflux disease. Three observation groups were formed: first — *H. pylori*-positive patients with eradication therapy; second — *H. pylori*-positive patients without eradication therapy; third — *H. pylori*-negative patients. The dynamics of clinical symptoms and erosive changes in the esophagus were assessed. ***Results.*** When comparatively assessing the clinical course of GERD in the groups of *H. pylori*-infected and *H. pylori*-negative patients, no significant differences were identified. Heartburn and epigastric pain were noted with equal frequency in both groups, belching was significantly more often observed in the group of *H. pylori*-negative patients, and vomiting, on the contrary, was slightly more common in the group of *H. pylori*-positive patients. The frequency of endoscopic signs of relapse of erosive esophagitis after 12–24 months was also comparable in the compared groups: 7/20 (35.0%) in the group with eradication therapy and 8/20 (40.0%) without eradication therapy. At the same time, the lowest relapse rate of 4/14 (26.8%) was noted in the group of *H. pylori*-negative patients. ***Conclusions.*** *Helicobacter pylori* does not have a significant protective or negative effect on the course of the erosive form of gastroesophageal reflux disease in school-age children.

Keywords: *gastroesophageal reflux disease, children, H. pylori*

ВЛИЯНИЕ ЭРАДИКАЦИОННОЙ ТЕРАПИИ *HELICOBACTER PYLORI* НА ТЕЧЕНИЕ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ У ДЕТЕЙ ШКОЛЬНОГО ВОЗРАСТА

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Резюме. *Введение.* Данные о роли *Helicobacter pylori* (Hp) в развитии гастроэзофагеальной рефлюксной болезни противоречивы. Большинство исследователей считают, что инфекция *H. pylori* оказывает защитный эффект на заболеваемость гастроэзофагеальной рефлюксной болезни (ГЭРБ). Неоднозначные результаты получены и в отношении влияния эрадикации *H. pylori* на развитие ГЭРБ, рефлюкс-эзофагита и симптомов, связанных с рефлюксом. В большинстве метаанализов не выявлено существенных различий в развитии ГЭРБ после эрадикации *H. pylori* между пациентами с эрадикацией и пациентами с персистирующей инфекцией. Но в ряде работ сообщено о значительном повышении риска ГЭРБ после успешной эрадикационной терапии. Большинство исследований проведено на когорте взрослых пациентов. Данные о влиянии *H. pylori* на течение ГЭРБ у детей фрагментарные. ***Цель*** — оценить влияние эрадикацинной терапии на течение гастроэзофагеальной рефлюксной болезни у детей школьного возраста. ***Материалы и методы.*** В исследование включено 55 детей от 7 до 17 лет 11 месяцев (средний возраст 11,4±2,1 года) с эрозивной формой гастроэзофагеальной рефлюксной болезни. Сформировано три группы наблюдения: первая — *H. pylori*-позитивные пациенты с проведеннной эрадикационной терапией, вторая — *H. pylori*-позитивные пациенты без эрадикационной терапии, третья — *H. pylori*-негативные пациенты. Оценивалась динамика клинических симптомов и эрозивных изменений в пищеводе. ***Результаты.*** При сравнительной оценке клинического течения ГЭРБ в группах *H. pylori*-инфицированных и *H. pylori*-негативных пациентов значительных отличий не выявлено. Изжога и эпигастральная боль отмечались с равной частотой в обеих группах. Отрыжка достоверно чаще отмечалась в группе *H. pylori*-негативных пациентов, а рвота, наоборот, несколько чаще в группе *H. pylori*-позитивных пациентов. Частота эндоскопических признаков обострения эрозивного эзофагита через 12–24 месяца была также сопоставима в сравниваемых группах: 7/20 (35,0%) в группе с проведенной эрадикационной терапией и 8/20 (40,0%) без эрадикационной терапии. При этом наименьшая частота рецидивов 4/15 (26,8%) отмечена в группе *H. pylori*-негативных пациентов. ***Выводы.*** Эрадикация *H. pylori* не оказывает значимого протективного или негативного эффекта на течение эрозивной формы гастроэзофагеальной рефлюксной болезни у детей школьного возраста.

Ключевые слова: *гастроэзофагельная рефлюксная болезнь, дети, H. pylori*

INTRODUCTION

There are conflicting data on the role of *H. pylori* in the development of gastroesophageal reflux disease (GERD). In 1997, J. Labenz et al. first suggested the hypothesis that eradication of *H. pylori* could lead to the development of reflux disease. And over the last 30 years, many studies have shown that H. pylori infection is negatively correlated with GERD. Moreover, most researchers believe that *H. pylori* infection has a protective effect on the incidence of GERD in general [1–3].

Conflicting results have also been obtained regarding the impact of *H. pylori* eradication in relation to the development of GERD, reflux esophagitis and reflux-related symptoms [4–6]. Xie et al. performed a meta-analysis of cohort studies and reported a significantly increased risk of GERD in patients with successful eradication compared to those with failed eradication (relative risk (RR) 1.70, 95% confidence interval (CI) 1.30–2.23), and a significantly increased risk in patients receiving eradication therapy compared to those receiving placebo (RR 1.99, 95% CI 1.23–3.22) [7]. One recent meta-analysis from 2020 also showed that *H. pylori* eradication therapy increased the risk of reflux esophagitis whether there were previous cases of esophagitis (OR 1.46, 95% CI 1.16–1.84, p=0.01) or *de novo* reflux esophagitis (OR 1.42, 95% CI 1.01–2.00, p=0.03). This fact was specific for all studies, especially in Western populations [8]. However, most meta-analyses have not found significant differences in the development of GERD after *H. pylori* eradication between patients with eradication and patients with persistent infection [9–11]. Nevertheless, Maastricht VI, recommends eradication therapy for patients with GERD, taking into account that *H. pylori* is a first class carcinogen [12]. As for children, the relationship between *H. pylori* and diseases of the upper digestive tract is probably even more complex. Thus, in contrast to adults, there is no association between *H. pylori* and functional dyspepsia [13]. Most of the works devoted to the relationship between GERD and *H. pylori* in children were performed in 2000–2010. A. Moon et al. (2009), in contrast to adults, showed a negative effect of *H. pylori* on the formation of reflux esophagitis in paediatric patients (mean age 8.2 years), the odds ratio was 5.79 compared to H. pylori-negative patients [14]. J. Brazowski et al. showed that Helicobacter pylori infection among children with acid gastroesophageal reflux does not affect the

prevalence of esophagitis. Thus, 13.8% of children in the group with *H. pylori* infection and 18.3% in the group without infection had esophagitis [15]. S.E. Zagorsky et al. also did not find any correlation between clinical symptoms of GERD, *H. pylori* and increased risk of erosive-ulcerative lesions of the oesophagus in children and adolescents. The authors based their study on medical check-ups of 300 patients and *H. pylori* [16]. Paediatric clinical guidelines for patients do not include recommendations for eradication therapy in children with GERD, resulting in the necessity to make an independent decision on eradication therapy in this group of patients [17]. Thus, studies on the relationship between GERD and *H. pylori* infection remain relevant.

AIM

To evaluate the effect of eradication therapy on the course of gastroesophageal reflux disease in school children.

MATERIALS AND METHODS

The study included 55 children from 7 to 17 years 11 months (11.4±2.1 years) with erosive form of gastroesophageal reflux disease. The main inclusion criteria: newly diagnosed symptoms of dyspepsia, erosive changes in the oesophagus according to fibrogastroduodenoscopy in children. Helicobacteriosis was diagnosed on the basis of a positive result of histological and/or rapid urease test ("Helicobacter-test" of the Research Institute of ECF, St. Petersburg). Initially all patients were divided into two groups: the first — *H. pylori*-positive (40 children), the second — *H. pylor*i-negative (15 children). Further, patients were divided into two more groups (20 patients in each), depending on the treatment tactics. Additional inclusion criteria for the first group: eradication therapy, control endoscopic examination in 12–24 months, absence of *H. pylori* according to histological or rapid urease test. Additional inclusion criteria in the second group: absence of eradication therapy, control endoscopic examination in 12–24 months. The final comparison was carried out among three groups of patients: the first — *H. pylori*-positive with eradication therapy (*H. pylori*+, eradication therapy+), the second — *H. pylori*-positive without eradication therapy (Hp+, eradication therapy-), the third — *H. pylori*-negative patients (Hp–). The dynamics of clinical symptoms and erosive changes in the oesophagus were evaluated. All obtained data were statistically processed by means of STATISTICA v.6.1 (StatSoft Inc.) application software package. Significance analysis of differences in qualitative features was performed using the χ^2 criterion. Differences at $p < 0.05$ were considered as significant.

RESULTS

No significant differences were found between clinical features of GERD in *Hp*-infected and *Hp*-negative patients. Heartburn and epigastric pain were noted with equal frequency in both groups. Belching was significantly more frequent in the group of *Hp*-negative patients, and vomiting, on the contrary, was slightly more frequent in the group of Hp-positive patients. In addition, stool disorders in the form of constipation, diarrhoea and their combination were significantly

Table 1. Comparative characteristics of symptoms in the groups of Hp-positive and Hp-negative patients with the erosive form of gastroesophageal reflux disease

Таблица 1. Сравнительная характеристика симптомов в группах Hp-позитивных и Hp-негативных пациентов с эрозивной формой гастроэзофагеальной рефлюксной болезни

Симптом / Symptom	Hp-позитивные / Hp-positive (n=40)	Hp-негативные / Hp-negative (n=15)	p
Эпигастральная боль / Epigastric pain	36 (90,0%)	14 (93,3%)	0,702
Изжога / Heartburn	15 (37,5%)	7 (46,6%)	0,537
Тошнота / Nausea	18 (45,0%)	3 (20,0%)	0,090
Отрыжка / Burping	12 (30,0%)	9 (60,0%)	**0,042**
Рвота / Vomiting	7 (17,5%)	0 (0,0%)	0,083
Раннее насыщение / Early satiation	2 (5,0%)	1 (6,6%)	0,809
Нарушения стула (запоры/диарея) / Of stool disorders (constipation/diarrhea)	7 (17,5%)	8 (53,3%)	**0,008**

Table 2. Dynamics of the main symptoms before and after treatment in the compared groups

Таблица 2. Динамика основных симптомов до и после лечения в сравниваемых группах

Группы наблюдения / Monitoring groups	Симптом / Symptom	До лечения / Before treatment	После лечения / After treatment	p
Hp+ эрадикационная терапия + / Hp+ eradication therapy +	Боли / Pain	19 (95,0%)	20 (100,0%)	0,312
	Изжога / Heartburn	6 (30,0%)	3 (15,0%)	0,256
	Отрыжка / Belching	6 (30,0%)	6 (30,0%)	1,000
	Тошнота / Nausea	10 (50,0%)	6 (30,0%)	0,197
	Рвота / Vomit	3 (15,0%)	0 (0,0%)	0,072
	Чувство раннего насыщения / Feeling of early satiety	0 (0,0%)	0 (0,0%)	–
	Нарушения стула* / Stool disorders*	3 (15,0%)	1 (5,0%)	0,292
Hp+ эрадикационная терапия– / Hp+ eradication therapy–	Боли / Pain	17 (85,0%)	16 (80,0%)	0,678
	Изжога / Heartburn	9 (45,0%)	8 (40,0%)	0,750
	Отрыжка / Belching	6 (30,0%)	6 (30,0%)	1,000
	Тошнота / Nausea	8 (40,0%)	5 (25,0%)	0,312
	Рвота / Vomit	4 (20,0%)	0 (0,0%)	**0,036**
	Чувство раннего насыщения / Feeling of early satiety	2 (10,0%)	2 (10,0%)	1,000
	Нарушения стула* / Stool disorders*	4 (20,0%	4 (20,0%)	1,000
Hp–	Боли / Pain	14 (93,3%)	13(86,6%)	0,736
	Изжога / Heartburn	7 (46,6%)	8 (53,3%)	0,744
	Отрыжка / Belching	9 (60.0%)	4 (26,6%)	0,092
	Тошнота / Nausea	3 (20,0%)	2 (13,3%)	0,633
	Рвота / Vomit	0	1 (6,7%)	0,312
	Чувство раннего насыщения / Feeling of early satiety	1 (6,7%)	0 (0,0%)	0,312
	Нарушения стула* / Stool disorders	8 (53,3%)	2 (13,3%)	**0,029**

* Запор и/или диарея.

* Of stool disorders (constipation/diarrhea).

Table 3. Frequency of exacerbations according to fibrogastroduodenoscopy in the compared groups after 12–24 months

Таблица 3. Частота обострений по данным фиброгастродуоденоскопии в сравниваемых группах через 12–24 месяца

Стадия заболевания / Stage of the disease	Группа 1 (Hp+, эрадикационная терапия+) / Group 1 Hp+ eradication therapy + (n=20)	Группа 2 (Hp+, эрадикационная терапия–) / Group 2 Hp+ eradication therapy– (n=20)	Группа 3 / Group 3 (Hp–) (n=15)
Обострение / Aggravation	7 (35,0%)	8 (40,0%)	4 (26,8%)
Ремиссия / Remission	13 (65,0%)	12 (60,0%)	11 (73, 2%)
p	p_{1-2}=0,744		p_{1-3}0,600 p_{2-3}=0,051

more frequent in the group of Hp-negative patients. The results are presented in Table 1.

Subsequently, there was evaluated the dynamics of the main clinical symptoms in 12–24 months. The proportion of patients with complaints of heartburn, nausea, vomiting and stool disorders slightly decreased in the group of Hp-positive patients with the course of eradication therapy after the control period. However, the differences were statistically unreliable. The dynamics of symptoms in two other groups (*Hp*-negative patients and *Hp*-positive patients without eradication therapy) was also insignificant. Significant differences concerned individual symptoms only. The results are presented in Table 2.

The assesment of control endoscopic examination showed that the frequency of recurrence of erosive esophagitis in the group of *Hp*-negative patients without eradication therapy was 8/20 (40,0%), which corresponded to the frequency of recurrence in the group of Hp-positive patients with eradication therapy — 7/20 (35,0%) (p=0,744). At the same time, the frequency of exacerbations was slightly lower in the group of *Hp*-negative patients — 4/15 (26.8%). The results are presented in Table 3.

DISCUSSION

No significant differences were found between *Hp*-positive and *Hp*-negative patients when assessing the severity of clinical symptoms of GERD. Epigastric pain and heartburn were noted with equal frequency in the groups of *Hp*-positive and *Hp*-negative patients. Belching was more frequent among GERD symptoms in Hp-negative patients. Associated stool disorders in the form of constipation, diarrhoea and their combination were also more characteristic for *Hp*-negative patients. Significant differences in the dynamics of symptoms in 12–24 months in the groups of *Hp*-positive patients after eradication therapy and without it were not observed.

The frequency of endoscopic signs of recurrence of erosive esophagitis after 12–24 months was also similar in the compared groups: 7/20 (35,0%) in the group with eradication therapy and 8/20 (40,0%) without eradication therapy. The lowest recurrence rate of 4/15 (26.8%) was observed in the group of Hp-negative patients. Thus, eradication therapy had no significant positive or negative effect on the recurrence rate in children with erosive GERD.

CONCLUSION

H. pylori eradication has no significant protective or negative effect on the course of erosive gastroesophageal reflux disease in school children.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

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QUALITY LIFE IN CHILDREN WITH ADENOID HYPERTROPHY

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Abstract. ***Introduction.*** Assessing the quality of life of children with adenoid hypertrophy is a significant multidisciplinary a problem of modern medicine that has a significant impact on the quality of life of children through such phenomena as snoring, sleep apnea, night terrors, sleeping with the mouth open, etc., which is determines the relevance of our research. Adenoid hypertrophy affects the quality of life of children not only in relation to sleep, but also in other aspects. ***Purpose of the study:*** analysis of the quality of life in children with adenoid hypertrophy. ***Research methods:*** we developed an original questionnaire based on principles for assessing the quality of life of children. Parents of patients aged 2 to 10 years suffering from hypertrophy adenoids, were asked to rate their child's quality of life on a 10-point scale, where 1 is very bad, and 10 is excellent. The main group included 202 children. The comparison group included 51 healthy children, whose parents answered questions at clinic No. 4 in Belgorod, where they applied for the purpose of immunization and/or admission to the sports section. Comparison of the main group and the control group was carried out using the Student's test. The significance control point is $p \leq 0.001$ for the main results. ***Results.*** None of the parents of children from the main group rated their child's quality of life as 10 points out of 10, and more than half (108, 53.5%) rated the quality of life as low or below average (up to 5 points out of 10). A very poor quality of life (1–2 points out of 10) was noted in every tenth child (24, 11.9%). Unlike the main group, in the comparison group a score of 6 points was noted in only one child, and in the vast majority of cases (43, 84.3%) 9–10 points were given. Thus, as a result of the study, a high degree of significance difference ($p < 0.001$) was obtained between the main group and the comparison group according to the Student's test, which indicates a serious decrease quality of life of children with adenoid hypertrophy, according to their parents.

Keywords: *quality of life, adenoid hypertrophy, children*

ОЦЕНКА КАЧЕСТВА ЖИЗНИ ДЕТЕЙ С ГИПЕРТРОФИЕЙ АДЕНОИДОВ

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Резюме. ***Введение.*** Оценка качества жизни детей с гипертрофией аденоидов — значимая многопрофильная проблема современной медицины, оказывающая значительное влияние на качество жизни детей посредством таких явлений, как храп, остановка дыхания во сне, ночные страхи, сон с открытым ртом и т.д., что и обусловливает актуальность нашего исследования. Гипертрофия аденоидов влияет на качество жизни детей не только в отношении сна, но и в других аспектах. ***Цель исследования:*** анализ качества жизни у детей с гипертрофией аденоидов. ***Методы исследования:*** мы разработали оригинальный опросник для оценки качества жизни детей. Родители пациентов от 2 до 10 лет, страдающих гипертрофией аденоидов, должны были оценить качество жизни своего ребенка по 10-балльной шкале, где 1 — очень плохое, а 10 — отличное. В основную группу были включены 202 ребенка. В группу сравнения вошел 51 здоровый ребенок, родители которых отвечали на вопросы в поликлинике № 4 г. Белгорода, куда обращались с целью иммунизации и/или допуска в спортивную секцию. Сравнение основной группы и группы контроля проводилось по критерию Стьюдента. Контрольная точка достоверности — p ≤0,001 основных результатов. ***Результаты.*** Ни один из родителей детей из основной группы не оценил качество жизни своего ребенка на 10 баллов из 10, а более половины (108, 53,5%) оценили качество жизни как низкое или ниже среднего (до 5 баллов из 10). Очень плохое качество жизни (1–2 балла из 10) отмечалось у каждого десятого ребенка (24, 11,9%). В отличие от основной, в группе сравнения оценка в 6 баллов отмечена лишь у одного ребенка, а в подавляющем большинстве случаев (43, 84,3%) выставлены 9–10 баллов. Таким образом, в результате проведенного исследования была получена разница высокой степени достоверности (p <0,001) между основной группой и группой сравнения по критерию Стьюдента, которая свидетельствует о серьезном снижении качества жизни детей с гипертрофией аденоидов, по мнению их родителей.

Ключевые слова: *качество жизни, гипертрофия аденоидов, дети*

INTRODUCTION

Quality of life can be simply defined as the area of human life that directly concerns the person and is important to him or her [1].

As a rule, the questionnaire method is used to determine the level of quality of life. General-purpose questionnaires can be used when studying large population groups with various pathologies. In this way, the results can be compared with each other, regardless of whether the humans are healthy or suffer from some disease, or if the groups of subjects are numerically different. However, general-purpose surveys are not useful tools for assessing individual changes that occur in each specific person [2].

Quality of life assessment allows to clarify the level of satisfaction of people with chronic diseases [3]. The study involved preschool children with chronic hypertrophy of adenoids. As a result of questioning the parents of these children, a sharp decrease in their quality of life was revealed, as well as the specifics of the focus of complaints in children of different constitutional types [4].

To study the quality of life of patients suffering from some pathology, in most cases modified surveys are developed based on the classic ones recommended by WHO. For example, to evaluate the quality of life of children of different ages, the QUALIN questionnaires are used [3, 5].

Chronic adenoid hypertrophy, being one of the leading problems of modern pediatrics, affects the somatic and functional development of the child i.e. changes the quality of his life [6].

In pediatric otolaryngology (ENT), adenoid hypertrophy is one of the most common reasons for seeking medical attention and accounts for up to 45% of ENT pathologies. According to published data, the vast majority of preschool and primary school children suffer from adenoid hypertrophy of varying degrees of severity. Age-related anatomical and physiological characteristics of the structure of the respiratory tract, can have a significant impact on quality of life [7].

It is reliably known that such life-threatening situations as obstructive sleep apnea occur in children with adenoid hypertrophy much more often than in the general population — up to 27% [4].

Disturbance of the structure and mechanisms of sleep, including those associated with adenoid hypertrophy, can lead to cognitive impairments such as learning disabilities, memory difficulties, problems with logical thinking, delay of the acquisition of new skills, as well as emotional and behavioral disorders such as anxiety and depression, apathy, irritability, obsessional states, and tics [8].

Adenoid hypertrophy affects the quality of life of children not only in relation to sleep, but also in other aspects: somatic, neuropsychological, cosmetic, etc. [9]. For example, it has been shown that the negative impact of adenoid vegetations on the body at the current level is considered not only as a

source of infection, but also as a manifestation of an immunodeficiency state and is carried out in three ways:

- mechanical obstruction caused by a hypertrophied pharyngeal tonsil;
- disruption of reflex connections;
- the presence of infection in tissue of the adenoids [10].

Most children and adolescents with chronic adenoid hypertrophy have functional disorders of the cardiovascular system and its autonomic regulation, referred to as the rhinocardial reflex. In adolescents with autonomic dysfunction, the degree of nasopharyngeal tonsil hyperplasia directly correlates with vegetovascular dystonia [11].

The works of A.V. Bykova et al. (2022), U.B. Mukhitdinova et al. (2017) show a close relationship between adenoid hypertrophy and otitis media, leading to an even greater decrease in the quality of life of children [12, 13].

In the literature, we came across several studies that focus on quality of life of patients with adenoid hypertrophy [1]. In the work of D.I. Stolyarov [14], using the standardized questionnaire "SF-36 HEALTH STATUS SURVEY", the physical and psychological components of assessment quality of life of patients with adenoid hypertrophy were studied. It was shown that the degree of hypertrophy of the nasopharyngeal tonsil does not have a significant effect on the quantitative indicators of the physical component of children's health. However, adenoid hypertrophy leads to a decrease in the indicators of the mental component and a progressive deterioration in the quality of life with age.

I.A. Zhmakina et al. (2017), used in their study the questionnaire "Pediatric Quality of Life InventoryTM", and showed, that physical development, adaptive resources and the tension of vegetative regulation of patients with adenoid hypertrophy were evaluated. G. Tastanova et al. considered in their article the physical development of primary school children with pathology of the adenotonsillar system [15].

Adenoid hypertrophy complicated by middle ear pathology can lead to serious psychoemotional problems, changes in speech production and, accordingly, a decrease in the quality of life and learning outcomes [16]. The disease affects the formation of the facial skeleton (adenoid face), malocclusion [17].

Thus, adenoid hypertrophy is a significant multidisciplinary problem of modern medicine that has a major impact on the quality of life of children, which determines the relevance of our research.

AIM

The aim of the study is to analyze the quality of life in children with adenoid hypertrophy.

MATERIALS AND METHODS

We developed an original questionnaire to assess the quality of life of children. Among other questions, parents of patients aged 2 — 10 years suffering from adenoid hypertrophy had to evaluate their child's quality of life on a 10-point scale, where 1 is very bad and 10 is excellent.

Inclusion criteria: children aged 2–10 years, no other chronic diseases that could affect the patient's quality of life.

Exclusion criteria: other age groups, presence of chronic diseases.

The main group included 202 children: 128 boys and 74 girls (M:F — 1,7:1). All children were treated at the Children's Regional Clinical Hospital in Belgorod for adenoid hypertrophy.

The comparison group included 51 healthy children whose parents answered questions at outpatient clinic No. 4 in Belgorod, where they applied for the purpose of immunization and/or admission to the sports section.

Comparison of the main group and the control group was carried out using the Student's t-test. The significance control point is $p \leq 0{,}001$.

RESULTS AND DISCUSSION

The opinion of parents about the quality of life in children in the main group and comparison group is presented in Table 1.

Thus, none of the parents of children in the main group rated their child's quality of life as 10 points out of 10, and more than half (108, 53,5%) rated the quality of life as low or below average (up to 5 points out of 10). A very bad quality of life (1–2 points out of 10) was noted by every tenth child (24, 11,9%). Unlike the main group, in the controls, a score of 6 points was noted in only one child, and in the vast majority of cases (43, 84,3%), 9–10 points were given.

As it is shown in Fig. 1, only 43 parents (21,3%) reported good quality of life (8–9 points). The remaining respondents noted a significant decrease in quality of life, in the overwhelming majority of cases directly related to adenoid hypertrophy (159, 78,7%), in contrast to the control group.

For clarity, we ranked the point score in Fig. 2 into three levels of quality of life: bad — 1–4 points, medium — 5–7 points, and good 8–10 points.

Table 1. Quality of life scores for children with adenoid hypertrophy and healthy children

Таблица 1. Балльная оценка качества жизни детей, страдающих гипертрофией аденоидов и здоровых детей

Баллы / Points	1	2	3	4	5	6	7	8	9	10
Основная группа / Main group	14	10	16	25	43	26	25	26	17	0
Группа сравнения / Comparison group	0	0	0	0	0	1	3	4	16	27

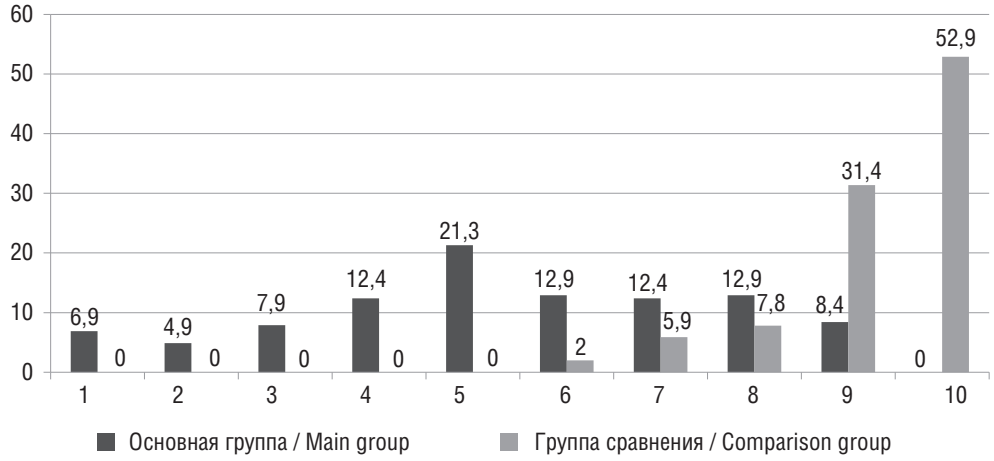

Fig. 1. Percentage assessment of the quality of life of children from the main group and comparison group on a 10-point scale

Рис. 1. Процентная оценка качества жизни детей из основной группы и группы сравнения по 10-балльной шкале

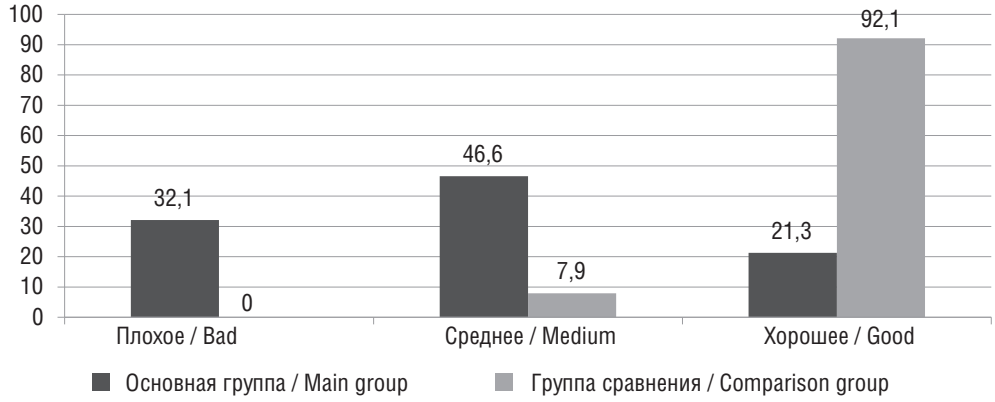

Fig. 2. Distribution of the obtained data into 3 levels of quality of life

Рис. 2. Распределение полученных данных на 3 уровня качества жизни

As can be seen from Fig. 2, in the main group, the quality of life of children suffered considerably compared to the controls with a high degree of significance — p <0.001 according to the Student's t-test.

CONCLUSION

Thus, as a result of the conducted study, a high degree of significance difference (p <0,001) was obtained between the main group and controls according to the Student's t-test, which indicates a serious decrease in the quality of life in children with adenoid hypertrophy, according to their parents. The results justify the need to develop new methods of early diagnosis, treatment and ranking of indications for conservative and surgical treatment of adenoid hypertrophy in children.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising

the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. The authors received written consent from the respondents to publish the data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие анкетируемых на публикацию данных.

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QUALITY OF LIFE IN YOUNG CHILDREN WITH FOOD ALLERGY

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Abstract. ***Introduction.*** Food allergy is a serious health problem in children. Quite often, parents underestimate it. Sometimes it leads to the exclusion of some important foods. Food allergy also causes stress, anxiety and even depression in parents and reduces the family's quality of life. The adapted and validated FAQLQ-PF questionnaire has been used in our comprehensive study of the quality of life in young children with food allergy. ***Aims the purpose*** of our study is to rate the quality of life of children with food allergy. ***Materials and methods.*** A prospective cohort observational study was conducted. An online electronic questionnaire was developed containing questions from the FAQLQ-PF questionnaire for parents of children aged 0–5 years with confirmed food allergy. ***Results.*** We obtained 45 questionnaires. The average age of the children was 3.14 years, among them 25 (44.4%) boys and 20 (55.6%) girls. Most parents/legal guardians rated their own general health, their children's health, as good or fair. 67% of respondents had a significant degree of concern and 69% stress due to the presence of food allergy in their children. 69% of parents were dissatisfied with dietary restrictions for children, and this factor was significant for 9.6% of respondents. 16.7% of children were afraid to try new food unfamiliar to them and experienced stress about this. Children with food allergy were significantly dissatisfied with their social restrictions in 19.5%, compared with their peers, they were more restless (13.4%), cautious (25%) and even less sociable (6.6%). ***Conclusions.*** The quality of life of children with food allergy is low not only due to the clinical manifestations of the disease, but also due to restrictive measures associated with the exclusion of food from the diet and reduced social activity.

Keywords: *food allergy, children, quality of life, questionnaire, early age*

КАЧЕСТВО ЖИЗНИ ДЕТЕЙ РАННЕГО ВОЗРАСТА С ПИЩЕВОЙ АЛЛЕРГИЕЙ

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Резюме. ***Введение.*** Пищевая аллергия у детей является серьезной проблемой для здоровья. Достаточно часто родители недооценивают ее, что может приводить к исключению некоторых важных продуктов питания и, соответственно, снижению качества жизни. Пищевая аллергия приводит также к стрессовым

ситуациям, беспокойству и депрессии у родителей, влияя на качество жизни всех членов семьи. ***Целью исследования*** стало изучение качества жизни у детей с пищевой аллергией и их родителей. ***Материалы и методы.*** Проведено проспективное когортное обсервационное исследование по комплексной оценке качества жизни пациентов с верифицированной пищевой аллергией. Была разработана электронная онлайн-анкета, содержащая вопросы из адаптированного и валидизированного опросника FAQLQ-PF. Анкетирование выполнено у родителей детей в возрасте от 6 месяцев до 5 лет (n=45) с подтвержденной пищевой аллергией. ***Результаты.*** Средний возраст детей составил 3,14 года, среди них 25 (44,4%) мальчиков и 20 (55,6%) девочек. Большинство родителей/законных представителей (67%) оценивали свое собственное общее состояние здоровья и здоровье детей как хорошее или удовлетворительное. Несмотря на это, у родителей наблюдалась значительная степень обеспокоенности из-за наличия пищевой аллергии у их детей, а также наблюдались стрессовые ситуации (69%). Родители были недовольны диетическими ограничениями у детей в 9,6% случаев. При этом дети боялись пробовать незнакомую им пищу и испытывали по данному поводу стресс (16,7%). При пищевой аллергии наблюдались социальные ограничения (19,5%), такие как участие в совместных посещениях семейных мест отдыха, включая вечеринки и фуд-корты торговых центров, дошкольных мероприятиях, включающих совместный прием пищи (36,6%). По сравнению со своими сверстниками пациенты были достоверно беспокойными (13,4%), осторожными (25%) и менее общительными (6,6%). ***Заключение.*** Качество жизни детей с пищевой аллергией низкое не только из-за клинических проявлений заболевания, но и ввиду ограничительных мероприятий, связанных с исключением продуктов питания в рационе и снижения социальной активности.

Ключевые слова: *пищевая аллергия, дети, качество жизни, опросник, ранний возраст*

INTRODUCTION

Food allergy (FA) is a hypersensitivity reaction to food that causes a variety of allergic symptoms. The prevalence of food allergy has increased dramatically, with some calling it a "new epidemic". Recent studies [1] show that the prevalence has grown by almost 50% since 2007. An estimated 15 million people in the United States, including ethnic groups, suffer from food allergy [2]. According to the World Health Organization (WHO), FA occurs on average in 2,5% of the population [3]. Among young children, FA is common at 6–8%, and in adolescents, at 2–4% [4].

Food allergy is a serious health problem in children. Clinical manifestations of FA and the need to adhere to strict restrictive diet lead to a deterioration in the quality of life of both children and entire family.

Several attempts have been made to create a sensitive and valid instrument to assess the quality of life of children with FA and their families. Quality of life surveys are multidimensional questionnaires from the patient's or caregiver's perspective that evaluate physical, psychological, and social aspects [5]. Awareness of the risk of severe allergic reactions, including rare cases of fatal anaphylaxis, leads to anxiety and stress among patients with FA and their caregivers [6].

B.L. Cohen et al. in 2004, developed a preliminary survey with 17 questions to identify parental anxiety about FA in their children [7]. When analyzing 352 questionnaires, high validity of the survey was determined (Cronbach's alpha is 0.95).

In another study, 221 parents of children with FA aged 0 to 18 years were asked to fill out the Food Allergy Parent Questionnaire (FAPQ), containing 18 questions related to the diagnosis and course of food allergy in their child [8].

The European Academy of Allergy and Clinical Immunology (EAACI) has defined this survey as the preferred tool for assessing the quality of life of patients with FA aged 0 to 8 years [9]. It is a parent form of the food allergy quality of life questionnaire (FAQLQ-PF) for children aged 0–12 years, i.e. it involves questioning the patients' legal representatives. A feature of this survey is its high sensitivity in evaluating the quality of life and parental illness perceptions in their children.

Studying the quality of life in children with food allergy and their parents is a topical issue. Which determined the purpose of our study.

AIM

The aim of this study is to rate the quality of life in children with food allergies and their families.

MATERIALS AND METHODS

We developed an online electronic survey containing questions from the FAQLQ-PF questionnaire for parents of children aged 0–5 years. The questions from the survey were translated from English into Russian.

In our study, the questionnaire included 47 questions. 44 of the 47 questions were about the quality of life and psychological condition of children, level of anxiety of parents, and social life of the family. The survey addressed issues of general health of children, as well as their parents/legal representatives. Three questions included patient demographic data: sex, age, date of birth. Data collection was carried out from October 2023 to December 2023 in outpatient preventive institutions of Moscow.

Study design

A prospective cohort observational study was conducted. It was completely anonymous. Parents/legal representatives gave their informed consent in advance.

The inclusion criteria were:

- the presence of informed consent;
- children aged 0– 5 years inclusive at the time of the questionnaire;
- confirmed diagnosis of food allergy in children.

The exclusion criteria were:

- lack of informed consent;
- children over 5 years old at the time of the survey;
- no diagnosis of food allergy in children.

We also excluded those questionnaires from the analysis where parents did not provide all the necessary information.

Ethical review

The study was carried out with the Local Ethics Committee approval (Protocol No. 16–23 dated September 14, 2021), all research stages were in accordance with the legislation of the Russian Federation, international ethics standards and regulatory documents of research organizations.

Statistical analysis of the obtained results was performed using a Microsoft Excel 2021 (developer Microsoft, USA) software package and StatTech v.2.1.0 (developer Stattech LLC, Russia).

RESULTS AND DISCUSSION

A total of 49 parents/legal representatives of children with a confirmed diagnosis of food allergy participated in the survey. The study included data from 45 questionnaires. Note: diagnosis of FA is difficult. Some diagnostic techniques, such as component diagnostics and basophil activation test, are limited in use, and the latter lacks standardization [10].

The studied groups of children did not differ significantly by sex: 25 (44.4%) boys and 20 (55.6%) girls. The average age of children was 3.14 years (min — 6 months, max — 5 years).

The quality of life is traditionally studied using surveys. Currently, the Russian-language version of the special questionnaire The Food hypersensitivity famiLy ImPact (FLIP) is used in Russia to assess the quality of life of family members of a child with FA (IIS-FA — index of impact on family members of a patient with FA) [11]. According to the results of a 2015 study of the psychometric properties of the questionnaire, an average level of internal consistency was demonstrated (Cronbach's alpha is from 0,72 to 0,83). Despite the satisfactory reliability of this survey, researchers use IIS-FA to evaluate the quality of life of family members of children suffering from FA [12].

The adapted and validated FAQLQ-PF questionnaire has been used in our study [13]. The number of questions in the FAQLQ-PF questionnaire varies depending on the age of the children: 14 items (0–3 years), 25 items (4–6 years), or 30 items (7–12 years) with a response scale from 0 (minimal quality of life impairment) to 6 (maximum quality of life impairment).

There is currently no definite method of treatment to induce lifelong natural meal tolerance and cure food allergies. Available treatments only aim to reduce the incidence of anaphylaxis by allowing the child to tolerate small amounts of the offending food, usually accidentally eaten. New data confirm earlier introduction of allergenic foods to infants to reduce the incidence of food allergy. If standardized and widely implemented, this may lead to a decrease in the prevalence of food allergy [14, 15].

Parents/legal representatives rated their own general health as excellent in 8% of cases, good in 72% and bad in 20%. At the same time, they described the general health of their children as good in 74% of cases, fair in 20% and bad in 6% of cases. Reliable differences ($p < 0,001$) were obtained in the assessment of the general health between legal representatives and children. At the same time, the majority of respondents noted a significant degree of concern about the physical health of their children (67%) and every second one — about the presence of FA. On the contrary, the presence of FA in a child causes stress in 69% of the respondents themselves and in 10% of the respondents — for the whole family.

The level of anxiety of parents of children with FA was moderate. Most of all, parents were worried that their child could accidentally swallow food that could trigger an allergy or suffer a severe allergic reaction: 43,3 and 40,4% of respondents, respectively.

Most children were dissatisfied with dietary restrictions, and this factor was significant for 9,6% of respondents. Children were also afraid to try new food unfamiliar to them and experienced stress about this (16,7%). Parents noted a lack of variety in diet if their children due to FA.

Quite often, parents underestimate food allergies, sometimes leading to the exclusion of some important foods. This also causes stress, anxiety, and even depression in parents and affects the quality of life of the family. Modern diagnostic tests are useful when interpreted in the context of the medical history, but cross-reactivity and the inability to predict the severity of allergic reactions remain a major problem.

The analysis of the social life of families showed that the presence of FA in children did not limit (27%) or limited slightly (35%) the types of activities accepted for the family (visiting food outlets, resting places, preschool institutions, children's clubs, etc.). Visits to restaurants, food courts, as well as places of rest for the whole family became impossible for some of the respondents. In addition, children with FA are limited in joint activities with their peers, such as participation in family parties, preschool activities, including sharing food. Thus, children with FA themselves were significantly dissatisfied with their social restrictions compared to their peers, were more restless (in 1,4%), cautious (in 25%) and even less sociable (in 6,6%).

We also found that, on average, due to the presence of FA, children have to limit from 2 to 6 types of food (0–2 products — 40,9%; 3–6 products — 31,8%). More than half of the surveyed parents have hope that their child will be completely cured of FA and its symptoms in the future. Most children themselves wish that they had completely disappeared clinical manifestations of FA.

CONCLUSION

Thus, the quality of life of children with food allergies is reduced not so much by the clinical manifestations of the disease, but by restrictive measures associated with the exclusion of food products from the diet and a decrease in social activity.

Most parents assessed their own general health and the health of their children as good or fair. But a significant degree of concern about the presence of food allergies in their children led to a stressful situation in the family. Almost all parents were dissatisfied with the dietary restrictions of their children. However, this fact was significant for them less often than in the survey of children. Children were afraid to try new food unfamiliar to them and also experienced stress about this. In case of food allergies, there were social restrictions for the family in participating in visits to recreation areas, as well as preschool and school activities, including sharing food. Compared with their peers, patients were reliably restless, cautious and less sociable.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. The authors received written consent from the respondents to publish the data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие анкетируемых на публикацию данных.

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LATENT TUBERCULOSIS INFECTION IN CHILDREN AND ADOLESCENTS: PREVENTIVE TREATMENT ISSUES

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Abstract. Preventive chemotherapy (PCT) for latent tuberculosis infection (LTBI) is considered one of the ways to reduce the incidence of tuberculosis (TB) in the world. A number of issues of PCT in children have not yet been fully resolved, including the effectiveness of preventing the active form of tuberculosis, taking into account possible side effects. The purpose of the study was to evaluate the effectiveness of a course of PCT in children with latent tuberculosis infection based on the generally accepted main criterion (absence of disease for 2 years) and additional ones (dynamics of a test with the recombinant tuberculosis allergen (ATR), treatment tolerance and course completion). On the basis of the Anti-tuberculosis dispensary No. 3 in St. Petersburg, a cohort of children aged 0–17 years was analyzed — 150 people, taken for dispensary observation in group VI A (altered sensitivity to tuberculosis allergens according to the ATR or Mantoux test). All children underwent phthisiatric examination; 134 children were subject to preventive chemotherapy (positive ATR test), which the parents of 34 children refused. The children were divided into three groups: I group (55 people) children who do not have family contact with a TB patient; II group (45 people) — children in contact with a TB patient (children of the first and second groups received PCT) and children of the third group — 34 children did not receive PCT (refusal). As a result of comparison of the three groups, reliable data were obtained on the effectiveness of PCT according to the criteria of preventing the disease and reducing the results of the ATR test. In no case did any adverse events requiring drug discontinuation occur, which made it possible to achieve high rates of completion of preventive chemotherapy courses. The conclusion is made about the need for preventive work with refusing parents to form their adherence to preventive treatment.

Keywords: *latent tuberculosis infection; children; teenagers; preventive treatment*

ЛАТЕНТНАЯ ТУБЕРКУЛЕЗНАЯ ИНФЕКЦИЯ У ДЕТЕЙ И ПОДРОСТКОВ: ВОПРОСЫ ПРЕВЕНТИВНОГО ЛЕЧЕНИЯ

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Резюме. Одним из путей снижения заболеваемости туберкулезом (ТБ) в мире считается превентивная химиотерапия (ПХТ) латентной туберкулезной инфекции (ЛТИ). Ряд вопросов ПХТ у детей до сих до конца не решен, в том числе об эффективности предупреждения активной формы туберкулеза с учетом возможных побочных эффектов. Целью исследования было оценить эффективность курса ПХТ у детей с латентной туберкулезной инфекции на основе общепринятого основного критерия (отсутствие заболевания в течение двух лет) и дополнительных (динамика пробы с аллергеном туберкулезным рекомбинантным (АТР), переносимость лечения и завершенность курса). На базе Противотуберкулезного диспансера № 3 г. Санкт-Петербурга проанализирована когорта детей в возрасте от 0 до 17 лет: 150 человек, взятых на диспансерное наблюдение по VI А группе (измененная чувствительность к туберкулезным аллергенам по пробе с АТР или Манту). Всем детям было проведено фтизиатрическое обследование. 134 ребенка подлежали превентивной химиотерапии (положительная проба с АТР), от которой родители 34 детей отказались. Дети были разделены на три группы: I группа (55 человек): дети, не имеющие семейного контакта с больным ТБ; II группа (45 человек): дети из контакта с больным ТБ (дети I и II групп получили ПХТ) и III группа: 34 ребенка не получили ПХТ (отказ). В результате сопоставления трех групп получены достоверные данные об эффективности ПХТ по критериям предотвращения заболевания и снижения результатов пробы с АТР. Ни в одном случае не возникло нежелательных явлений, требовавших отмены препаратов, что позволило достигнуть высоких показателей завершенности курсов превентивной химиотерапии. Сделан вывод о необходимости профилактической работы с отказывающимися родителями для формирования их приверженности к профилактическому лечению.

Ключевые слова: *латентная туберкулезная инфекция, дети, подростки, превентивное лечение*

INTRODUCTION

According to the World Health Organization (WHO), in modern conditions the priority direction for reducing tuberculosis (TB) is the prevention and treatment of latent tuberculosis infection (LTBI) [1]. WHO experts believe that without addressing the challenge of LTBI diagnostics and treatment, the task of reducing tuberculosis incidence in all countries will not be solved [2, 3].

Latent tuberculosis infection is a condition in which mycobacterium tuberculosis (MBT) is present in the human body, causing positive reactions to immunological tests, including to TB allergens in the absence of clinical and radiological signs of tuberculosis [4]. Over the past decade, an intradermal test with a recombinant tuberculosis allergen (ATR or Diaskintest) containing MBT antigens: ESAT-6 and CFP-10 has been used in the Russian Federation to diagnose LTBI and TB, as well as to determine indications for preventive treatment of children. The ATR test (compared to the Mantoux test) allows for more effective identification of patients at high risk for developing tuberculosis [5–8]. Thus, according to E.M. Bogorodskaya et al., among children aged 8–17 years who fell ill in Moscow in 2021, 33 out of 43 (76,7%) were detected using screening with immunological tests before the onset of clinical manifestations of the disease (according to the results of an intradermal test with ATR) [9].

Due to their anatomical and physiological characteristics, children are most sensitive to TB infection and have a high risk of developing the disease, especially in the presence of comorbid pathology [10–12].

According to clinical guidelines existing in the Russian Federation, children with LTBI are recommended the reventive treatment with anti-tuberculosis drugs (ATDs): preventive chemotherapy (PCT) [4]. Traditionally, the effectiveness of preventive therapy is assessed by the main criterion — the absence of tuberculosis within two years after its implementation [4]. However, even in the absence of preventive treatment, 5–10% of infected persons are at risk of developing the disease, according to WHO data. This is why there are conflicting views on the issues of organizing preventive therapy, mandatory nature of its implementation, and search for effective and safe chemotherapy regimens using anti-tuberculosis drugs with high bactericidal activity continues [13–15].

In this regard, when choosing the tactics for managing children with LTBI, it is necessary to take into account the other possible criteria for the effectiveness and safety of chemotherapy: completion of PCT courses, tolerability of treatment in children, and dynamics of immunodiagnostic samples.

AIM

The aim of the study is to evaluate the effectiveness of preventive treatment courses in chil-

dren with LTBI, taking into account the main and additional criteria.

MATERIALS AND METHODS

A cohort of children (0–17 years old, n=150) observed in the dispensary department No. 1 of the Interdistrict Petrograd-Primorsky Anti-tuberculosis dispensary No. 3 in St. Petersburg in connection with MBT infection in the period from 2018 to 2021 was analyzed. The ratio of boys and girls was 56 and 44%, respectively (Table 1).

Inclusion criteria for the study: all children infected with MBT and registered in group VI A of medical follow-up. Exclusion criteria: presence of active tuberculosis. Of the 150 children, 134 had a TB positive ATR test result, the remaining 16 had a TB negative ATR test result and were referred with altered tuberculin sensitivity according to the Mantoux test with 2 tuberculin units (TU) (16 children aged 0 to 7 years). These 16 children were not indicated for preventive treatment, only observation. The remaining 134 children with indications for a course of chemotherapy (TB positive ATR test) were divided into three groups: group I — without established contact with a tuberculosis patient (n=55); group II included household contacts with a patient with active TB (n=45) and group III included children whose parents refused preventive treatment despite indications (n=34), including 14 from the foci of tuberculosis infection. Among tuberculosis contacts (children of group II), family contacts predominated 34 (75,6%): including 24 (53,3%) with a person with bacterial excretion. Among the 14 children in group III (who refused chemotherapy) and those with contact, 9 (64,3%) had family contacts, including 5 (35,7%) with a person with bacterial excretion. The remaining 5 (35,7%) children had no established tuberculosis contact.

All children underwent a full examination, which contains taking the anamnesis, including an epidemiological anamnesis, results of immunodiagnostics (Mantoux tests with 2 TU, ATR tests according to the indications of in vitro tests: QuantiFERON® or TB-FERON), radiological imaging, as well as laboratory tests.

To prevent the transition of LTBI to the active form of tuberculosis, children of groups I and II were prescribed PCT in accordance with the Federal Clinical Guidelines (FCG), a regimen of two anti-tuberculosis drugs: isoniazid (H) + pyrazinamide (Z) for 3–6 months in the absence of data on drug resistance (DR) at the source of infection. Children from contacts with DR to H (n=5) were administered rifampicin (R) for 4 months; in case of multiple drug resistance (MDR) (n=4), no treatment was carried out, only monitoring in accordance with the FCG [4].

The effectiveness of the PCT courses was assessed based on four criteria: absence of the disease for two years after the courses of PCT, completeness of the courses, tolerance to anti-tuberculosis drugs and dynamics of immunodiagnostic samples.

All parents gave voluntary informed consent for the study.

Statistical analysis was performed using MS Excel 2010 and the SPSS 17.0 software package. To determine the reliability of differences, Student's t-test for absolute values and Pearson's χ^2 test for relative variables were used. Statistical significance was considered at a level of $p < 0,05$.

RESULTS AND DISCUSSIONS

In 16 children (aged 0 to 7 years) who were referred to the anti-tuberculosis dispensary due to a change in tuberculin sensitivity according to the Mantoux test with 2 TU, ATR remained TB negative during dynamic monitoring without the prescription of PCT after 6–12 months. The results of the clinical and radiological examination did not reveal any pathology. Based on this, the children were removed from medical check-up and excluded from our further study.

Table 1. Age and sex composition of children infected with mycobacterium tuberculosi included in the study

Таблица 1. Возрастно-половой состав детей, инфицированных микобактериями туберкулеза, включенных в исследование

Разделение по половой принадлежности / Gender division	Возраст / Age			
	0–3 года / 0–3 years (n=12)	4–7 лет / 4–7 years (n=38)	8–14 лет / 8–14 years (n=59)	15–17 лет / 15–17 years (n=41)
Дети (муж.) / Children (men)	7 (58,3%)	20 (52,6%)	42 (71,2%)	15 (36,6%)
Дети (жен.) / Children (women)	5 41,7%)	18 (47,4%)	17 (28,8%)	26 (63,4%)

Table 2. Comprehensive assessment of the effectiveness and safety of preventive chemotherapy for latent tuberculosis infection in children

Таблица 2. Комплексная оценка эффективности и безопасности превентивной химиотерапии при латентной туберкулезной инфекции у детей

Критерии оценки эффективности / Performance evaluation criteria	Проведение ПХТ / Carrying out PCT		III группа (отказ от ПХТ) / III group (refusal from PCT) (n=34)
	I группа (без контакта с МБТ) / I group (without contact with MBT) (n=55)	II группа (с контактом с МБТ) / II group (with contact with MBT) (n=45)	
Заболевание в течение 2 лет / Illness for 2 years	1 (1,8%) P_{I-II}= 0,32401; *χ^2= 1,515	3 (6,7%) *P_{II-III}= 0,00932; *χ^2= 3,395	7 (20,6%) *P_{I-III}= 0,00445; *χ^2= 9,049
Нежелательные явления, связанные с приемом ПТП / Adverse events associated with taking PTPs	10 (18,2%) P_{I-II}= 0,10539; *χ^2= 3,030	15 (33,3%)	–
Гиперферментемия / Hyperenzymemia	6 (10,9%) P_{I-II}=1,00000; χ^2=0,001	5 (11,1%)	
Клинические симптомы со стороны ЦНС / Clinical symptoms from the central nervous system	4 (7,3%) *P_{I-II}=0,04312; *χ^2=4,594	10 (22,2%)	
Завершенность / Completeness	50 (90,9%) P_{I-II}=0,74143; χ^2=0,230	40 (88,9%)	
Завершенность с перерывами / Completeness with breaks	5 (9,1%) *P_{I-II}=0,02819; *χ^2=5,802	12 (26,7%)	
Уменьшение чувствительности к АТР / Decreased sensitivity to ATR	38 (69,1%) P_{I-II}=0,52782; χ^2=0,520	28 (62,2%) *P_{II-III}=0,00283; *χ^2=9,942	9 (26,5%) *P_{I-III}=0,00016; *χ^2=15,315

* Различия достоверны. / Differences are significant.

Thus, further analysis included 134 children with a TB positive ATR test when taken for medical follow-up.

The analysis of cases of the disease within two years after the course of PCT and other performance evaluation criteria are given in Table 2.

Within two years after the course of preventive chemotherapy, the disease was detected in 1 (1,8%) person in group I, 3 (6,7%) children in group II, and significantly more frequently in 7 (20,6%) children in group III. Based on the results of phthisiological diagnostics, the following forms of tuberculosis of the respiratory organs were established: tuberculosis of the intrathoracic lymph nodes (TITLN), primary tuberculosis complex (PTC), and focal pulmonary tuberculosis. Thus, in group I, TITLN was diagnosed in 1 child, in group II — TITN in 1 child and PTC in 2 children. In children of group III (who refused chemotherapy), TITLN was diagnosed in 6 children and focal tuberculosis was diagnosed in 1 child.

Analysis of the completion of the PCT courses showed that almost all children in groups I and II finished it entirely: 90,9 and 88,9%, respectively. The differences between groups are statistically insignificant (p >0,05).

The tolerability of PCT was significantly worse in children with tuberculosis contacts, including 3 patients who received an individual regimen: DR to H — R intake for 4 months. The frequency of adverse events (AE) during taking ATDs is presented in Table 2. At the follow-up examination during the intake of ATDs in children of group I, asymptomatic hyperenzymemia (increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST)) was observed in 10,9% of cases, and clinical symptoms from the central nervous system (CNS) were observed in 7,3%. In children of group II, hyperenzymemia was ob-

Table 3. Dynamics of immunodiagnostic samples of patients

Таблица 3. Динамика иммунодиагностических проб пациентов

Показатель / Index	I группа / Group I (n=55)	II группа / Group II (n=45)	III группа / Group III (n=34)
Увеличение папулы / Enlarged papule	10 (18,2%) P_{I-II}=1,00000; χ^2=0,053	9 (20%) *P_{II-III}=0,00001; *χ^2=20,377	24 (70,6%) *P_{I-III}=0,00001; *χ^2=24,443
Уменьшение папулы / Papule reduction	38 (69,1%) P_{I-II}=0,52782; χ^2=0,520	28 (62,2%) *P_{II-III}=0,00283; *χ^2=9,942	9 (26,5%) *P_{I-III}=0,00016; *χ^2=15,315
Без динамики / No dynamics	7 (12,7%) P_{I-II}=0,57747; χ^2=0,495	8 (17,8%) *P_{II-III}=0,00283; *χ^2=9,942	1 (2,9%) *P_{I-III}=0,07002; *χ^2=4,223
Частота гиперергических реакций до лечения / на момент взятия на учет (III группа) / Frequency of hyperergic reactions before treatment / at the time of registration (III group)	25 (45,4%) P_{I-II}= 0,68558; χ^2= 0,300	18 (40,0%) *P_{II-III}= 0,04108; *χ^2= 4,729	22 (64,7%) *P_{I-III}= 0,08578; *χ^2= 3,125
Частота гиперергических реакций после лечения / при контрольном обследовании (III группа) / Frequency of hyperergic reactions after treatment / during control examination (III group)	10 (5,4%) P_{I-II}=0.40481; χ^2=0,970	5 (11,1%) *P_{II-III}= 0,00026; *χ^2=14,577	17 (50,0%) *P_{I-III}=0,00211; *χ^2=10,065
Конверсия в отрицательный результат / Conversion to negative result	10 (18,2%) P_{I-II}=0,40481; χ^2=0,970	5 (11,1%) *P_{II-III}=0,00001; *χ^2=70,536	0 (0%) *P_{I-III}=0,00001; *χ^2=56,269

* Различия достоверны. / Differences are significant.

served in 11,1% of cases, and symptoms from the CNS were observed in 22,2%. Symptoms from the CNS included complaints of headache, drowsiness, fatigue (these changes were mild and short-lived). Hyperenzymemia was transient (an increase in enzymes to a level 20–30% above normal), did not require complete discontinuation of PCT, and was cured by hepatoprotective therapy (Liv-52, Karsil).

When assessing the dynamics of immunodiagnostic samples in children who received PCT, a decrease in the test with ATR was significantly more often observed compared to children without PCT, regardless of the presence of tuberculosis contact (Table 3).

The frequency of hyperergic reactions before treatment was higher in children from group I. According to the results of the treatment, a decrease in the frequency of hyperergy in children without tuberculosis contact by 8,4 times and in children with tuberculosis contact by 3,6 times was achieved. It is also worth noting that the average size of a papule before treatment was higher in children of group I. Conversion of the ATR test result was observed more often in children of the group I.

Thus, as a result of the work, high efficiency of the preventive treatment was established. It consisted primarily in preventing cases of transition LTBI to clinically expressed forms of tuberculosis within the next two years after PCT, as evidenced by a reliably high percentage of sick children in group III (refusal of PCT). Satisfactory tolerability of PCT in children of groups I and II, regardless of the presence of tuberculosis contact, should be noted: in no case were there serious AE requiring the discontinuation of PCT, which made it possible to achieve high rates of completion of PCT courses. It should be noted that the dynamics of the test with ATR are an important criterion for the effectiveness of preventive treatment. A clear effect of therapy was shown both in reducing the absolute values of the ATR test and in decrease the proportion of hyperergic reactions. On the contrary, in children of group III (refusal of PCT), where the number of sick people was higher, a decline in sensitivity to the test with ATR was significantly less common. Unmotivated refusals of parents from preventive treatment indicate insufficient work to form adherence to tuberculosis prevention [16]. Decreased sensitivity to ATR reduces the risk of developing a local form of TB in the future

and indications for the number of repeated preventive chemotherapy and shortens the duration of medical check-up [17].

CONCLUSION

1. Preventive chemotherapy covered 100 children (74,6%) out of 134 with a TB positive test with ATR, which is insufficient. The main reason is parental refusal, which requires strengthening preventive work to improve adherence to treatment.

2. As a result of the PCT course, more than half of the children achieved a decrease in the ATR test. The incidence of TB was significantly lower than in children without PCT (group III: refusals). Tolerability of therapy is satisfactory.

3. It is necessary to evaluate the effectiveness of PCT courses using not only the main (absence of TB for two years), but also additional criteria (completeness of courses, tolerability of anti-tuberculosis drugs and dynamics of the sample with ATR).

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных.

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AGE-RELATED ASPECTS OF AUTONOMIC-REGULATORY SUPPORT OF MORPHOFUNCTIONAL PROCESSES OF PUBERTY PERIOD IN HEALTHY ADOLESCENTS

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Abstract. ***Background.*** It is known that by adolescence, the basic neurohumoral mechanisms of autonomic regulation are considered complete. However, without understanding the age-related evolution of vegetative homeostasis, it is not possible to give an objective assessment of the correspondence of its level to the characteristics of pubertal processes. ***Purposes.*** To identify the patterns of dynamic changes in the system of vegetative homeostasis in children at the stages of postnatal ontogenesis to determine the degree of adequacy of the processes of controlling morphofunctional transformations of puberty. ***Materials and methods.*** A total of 145 healthy children were examined: 44 adolescents aged 13–17 made up the main group, 101 children from 1 year of age to 13 years were included in the comparison group. In this work, the method of heart rate variability analysis was used. ***Results.*** The article presents data on dynamic changes in the system of vegetative homeostasis, consisting in the transition from the predominance of centralization in young children to the dominance of controlling autonomy in the adolescent population. ***Conclusion.*** The revealed regularity is the basis of the postnatal ontogenetic development of vegetative-regulatory mechanisms for the formation of the optimal level of control of morphofunctional transformed processes of puberty.

Key words: *children, autonomic regulation, puberty*

ВОЗРАСТНЫЕ АСПЕКТЫ ВЕГЕТАТИВНО-РЕГУЛЯТОРНОГО ОБЕСПЕЧЕНИЯ МОРФОФУНКЦИОНАЛЬНЫХ ПРОЦЕССОВ ПУБЕРТАТНОГО ПЕРИОДА У ЗДОРОВЫХ ПОДРОСТКОВ

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Резюме. ***Введение.*** Известно, что к подростковому возрасту основные нейрогуморальные механизмы вегетативной регуляции считаются завершенными. Однако без понимания возрастной эволюции вегетативного гомеостаза дать объективную оценку соответствия его уровня характеристикам пубертатных процессов не представляется возможным. ***Цель исследования.*** Выявить закономерности динамических изменений в системе вегетативного гомеостаза у детей на этапах постнатального онтогенеза для определения степени адекватности процессов управления морфофункциональными преобразованиями периода поло-

вого созревания. ***Материалы и методы.*** Всего обследовано 145 здоровых детей: 44 подростка 13–17 лет составили основную группу, 101 ребенок от 1 года жизни до 13 лет вошли в группу сравнения. В работе использовался метод анализа вариабельности сердечного ритма. ***Результаты.*** В статье представлены данные о динамических изменениях в системе вегетативного гомеостаза, заключающихся в переходе от преобладания централизации у детей раннего возраста к доминированию управляющей автономии в подростковой популяции. ***Выводы.*** Выявленная закономерность — основа постнатального онтогенетического развития вегетативно-регуляторных механизмов по формированию оптимального уровня управления морфофункциональными преобразовательными процессами пубертатного периода.

Ключевые слова: *дети, вегетативная регуляция, пубертатный период*

INTRODUCTION

The formation of autonomic-regulatory structures in children occurs in accordance with the general patterns of maturation of the functional systems of the child's body [1–3]. It is known that by adolescence, the main neurohumoral mechanisms of autonomic regulation are considered complete [4–6]. However, without understanding the age-related evolution of vegetative homeostasis (VH), it is not possible to make an objective assessment of the correspondence of the level of regulatory effects on the processes of formation of the reproductive function [7–10]. At the same time, the issues of optimization of the control mechanisms of autonomic regulation at the stages of postnatal ontogenesis, ensuring the optimal level of morphofunctional processes of the puberty, remain insufficiently studied in the literature [11–13]. Obviously, the results of such studies would contribute to the early diagnosis of predictors of psychosomatic pathology, which often debut in children of this age group [14–17].

AIM

The aim of the study is to identify patterns of dynamic changes in the regulatory determinants of VH in children at the stages of postnatal ontogenesis in order to determine the degree of adequacy of the processes of controlling morphofunctional transformations of puberty, improving early diagnosis and targeted correction of their disorders.

MATERIALS AND METHODS

A comparative controlled study of dynamic changes in inter-circuit, central and autonomous dominance in the VH system was conducted in 145 healthy children. The main group consisted of 44 adolescents (boys — 18, girls — 17) aged 13–17. The comparison group included 101 children: 22 — first year of life, 35 — 4–7 years and 44 (boys — 19, girls — 25) aged 8–12 years. The number of children in all groups was comparable, the ratio of boys and girls did not differ significantly ($p > 0,05$). Gender differences were taken into account in the groups of adolescent children. Inclusion criteria: children attending preschool institutions and comprehensive schools (except for children of the first year of life) from I and IIa health groups (f-112). Unorganized children aged 1–3 years were excluded due to significant differences in living conditions. The examination was conducted in a children's clinic with the conditions for electrophysiological studies observed. Informed consent was obtained from all subjects and their parents.

The autonomic-regulatory parameters were studied by analyzing the heart rate variability (HRV) using the VNS-Micro vegetotester 2000 Hz. The recording was made on short sections (at least 500 cardiac cycles) with subsequent processing using the Poli-Spectrum (Neurosoft, Russia) program. Statistical analysis was performed using the STATISTICA 20 (USA) program and included the Mann-Whitney U and Kruskal-Wallis tests. To compare variables in independent groups, the bootstrap version of the Satterthwaite test (heteroscedastic version of the Student's t-test) was used. Differences were considered statistically significant at $p < 0,05$.

RESULTS

During the study, absolute values of the indicators of time and frequency analysis of HRV were compared, the results of which are shown in Fig. 1 and 2.

As it is shown in Fig. 1, the level of tension index SI, arbitrary units, and indicator of the adequacy of regulation processes AMo/Mo in children aged 13–17 years, compared with the data for children in the first year of life, significantly decreased: by 87,8 and 72,2% in the group of boys and by 87,3 and 73,2% in girls, respectively (all $p < 0.05$).

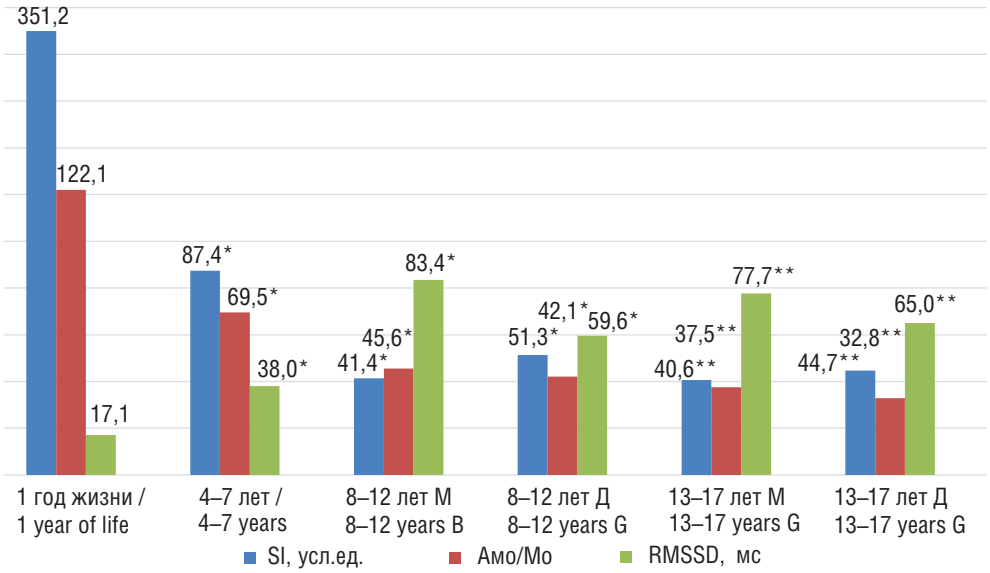

Fig. 1. Dynamic changes in absolute time region indicators of heart rate variability in healthy children, %. (Here and in Fig. 2 — statistical significance of the differences ($p < 0.05$): * — indicators of the age group to the data of the previous one; ** — data of the group 13–17 years old to the indicator of the first year of life; B — boys; G — girls; SI, arbitrary units — tension index, AMo/Mo — indicator of the adequacy of regulation processes, RMSSD, ms — representative indicator of parasympathetic activity.)

Рис. 1. Динамические изменения абсолютных значений показателей временной области вариабельности сердечного ритма у здоровых детей, %. (Здесь и на рис. 2 — статистическая значимость различий ($p < 0,05$): * — показателей возрастной группы к данным предыдущей; ** — данных группы 13–17 лет к показателю первого года жизни; М — мальчики, Д — девочки, SI, усл. ед. — индекс напряжения, AMo/Mo — показатель адекватности процессов регуляции, RMSSD, мс — репрезентативный показатель парасимпатической активности.)

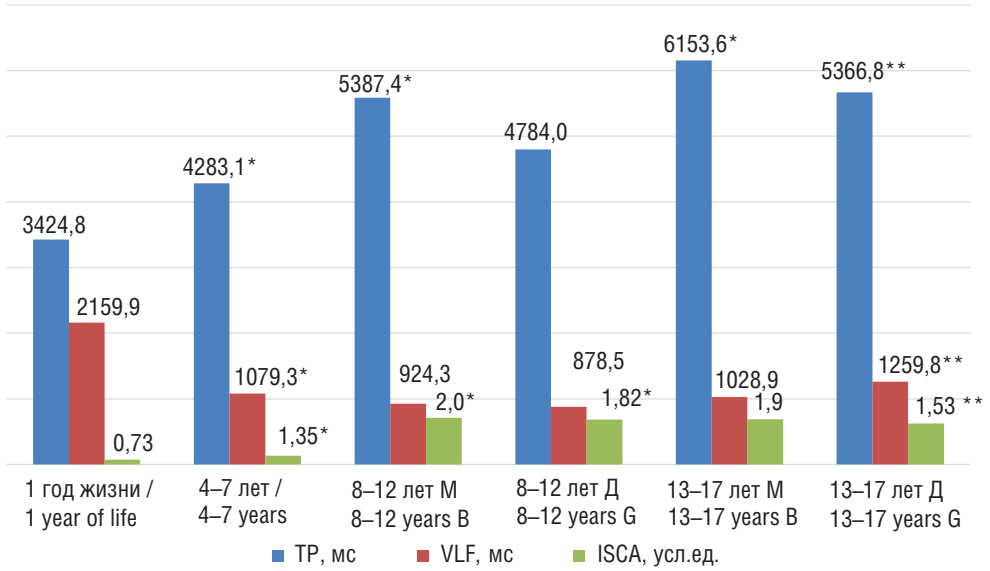

Fig. 2. Dynamic changes in absolute values frequency region indicators of heart rate variability in healthy children, %. TP, ms^2 — an indicator of the total power of waves in the heart rate variability spectrum; VLF, ms^2 — indicator of activity in the very low frequency range; ISCA — index of activation of subcortical structures

Рис. 2. Динамические изменения абсолютных значений показателей частотной области ВСР у здоровых детей. TP, $мс^2$ — показатель суммарной мощности волн спектра вариабельности сердечного ритма; VLF, $мс^2$ — показатель активности диапазона очень низких частот; ISCA — индекс активации подкорковых структур

As follows from the data in Fig. 2, by adolescence, children showed a significant change in the absolute values of the wave characteristics of HRV in the form of an increase in the total power of all ranges of the frequency spectrum of TR, ms^2 by 79,6 and 56,7% in boys and girls, respectively, which indicated the dominance of the autonomous circuit generations in the VH system (all

Table 1. Dynamic characteristics of the spectrum type in children of the examined groups, ms²

Таблица 1. Динамические характеристики типа спектра у детей обследованных групп, мс²

Возраст / Age	Показатели частот, мс² / Frequency indicators, ms²			Тип спектра / Spectrum type
	HF, мс² (ms²)	LF, мс² (ms²)	VLF, мс² (ms²)	
1 год / 1 year	9,0	33,9	57,1	VLF > LF > HF
4–7 лет / 4–7 years	40,8	32,1	27,1	VLF > HF > LF
8–12 лет / 8–12 years	49,0	31,7	19,3	HF > LF > VLF
13–17 лет / 13–17 years old	51,9	32,7	15,8	HF > LF > VLF

p <0,05). The revealed dynamic frequency shift towards the dominance of autonomy was accompanied by a weakening of the suprasegmental-segmental connection, as evidenced by an increased index of activation of subcortical structures ISCA by 2,5 and 2,1 times (all p <0,05). It should be emphasized that the reduction of biopotentials emanating from the very low frequency range VLF, ms² in children aged 13–17 years compared to the data of children in the first year of life: by 52,4 and 41,7% in boys and girls, respectively, indicated a significant decrease in energy-metabolic expenditure for regulatory processes (all p <0,05).

Table 1 provides information on the dynamics of relative values of regulatory parameters, so-called HRV spectrum type [3].

The data in the table indicate a high level of centralization in the control of functional systems in children in the first year of life, in which the dominant frequencies in the structure of the total power of spectrum waves (TP, ms²) are the biopotentials of the very low (VLF, ms²) and low (LF, ms²) frequency ranges. It has been shown that in the age group of 4–7 years, the influence of high-frequency oscillations (HF, ms²) in the regulatory process increases significantly, but by adolescence, the spectrum type begins to correspond to the optimal parameters (HF — 40–55%; LF — 25–35%, VLF — 6–15%) of frequency proportionality [8, 9].

It should be noted that in the groups of boys and girls, no reliable differences in the studied indicators that violate the general pattern of dynamic changes were revealed.

DISCUSSION

It is known that ergotropic tension associated with high energy-metabolic expenditures, typical for young children, is dictated by the high vulnerability of the organism and the incompleteness of the formation of regulatory adaptation mechanisms. At the same time, such high energy-metabolic expenditures associated with control centralization in adolescent children could cause overstrain of adaptation mechanisms and depletion of the functional reserve.

The results of the study allowed us to identify a significant pattern of transition of the control function of the VH from high centralization in young children to dominant autonomy in adolescents. The physiological evolutionary determinism of such a transformation is due to the transition from energy-consuming ergotropic activity to an energy-saving regime of inter-circuit dominant autonomy in the control of functional systems, creating optimal conditions for the adequacy of the level of autonomic regulation to the requirements of pubertal processes.

CONCLUSION

The revealed patterns are a conceptual basis for the postnatal ontogenetic maturation and development of the child's organism, and the transition to autonomy in the control of functional systems in adolescence should be considered the physiological essence of modulating the inter-circuit dominant. The results of the study may have not only theoretical significance, but also important practical application for pediatric practice as criteria for functional maturity and harmonious development of children at different age periods, as well as early diagnosis and correction of their disorders.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

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COMPARATIVE CHARACTERISTICS OF THE PERINATAL PERIOD AMONG CHILDREN BORN IN THE EARLY STAGES OF GESTATION USING ASSISTED REPRODUCTIVE TECHNOLOGIES AND SPONTANEOUS PREGNANCY COURSE

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Abstract. A retrospective study was conducted of 42 copy pairs of newborns born in St. Petersburg and the Leningrad region as a result of independent pregnancy and after the use of ART at 22 weeks. 0 days — 27 weeks. 6 days inclusive for the period 2018–2022 as a result of a singleton or multiple pregnancy (twins). Also, each group was divided into 2 subgroupsmore, according to gestational age. All 4 subgroups were compared with each other. Based on the study, it can be noted that the course of pregnancy and childbirth in children of the compared groups is ambiguous. Nevertheless, there is unity in the implementation of biological programs of growth and development, as well as a significantly low level of somatic and reproductive health in mothers who planned pregnancy using ART. It is planned to create an evidence-based algorithm that will help practicing doctors and future parents avoid undesirable consequences and minimize the risks to the life and health of newborns.

Keywords*: assisted reproductive technologies, deeply premature babies, premature birth, infertility, mortality of newborns*

СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА ТЕЧЕНИЯ ПЕРИНАТАЛЬНОГО ПЕРИОДА ДЕТЕЙ, РОЖДЕННЫХ НА РАННИХ СРОКАХ ГЕСТАЦИИ, С ИСПОЛЬЗОВАНИЕМ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ И САМОСТОЯТЕЛЬНОЙ БЕРЕМЕННОСТИ

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Резюме. Проведено ретроспективное исследование 42 пар-копий новорожденных детей, рожденных в Санкт-Петербурге и Ленинградской области в результате самостоятельной беременности и после приме-

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нения вспомогательных репродуктивных технологий (ВРТ) на сроке 22 недель 0 дней — 27 недель 6 дней включительно за период 2018–2022 гг. в результате одноплодной или многоплодной беременности (двойни). Каждую группу разделили также на еще 2 подгруппы по срокам гестации. Сравнивались все 4 подгруппы между собой. На основании проведенного исследования можно отметить неоднозначность течения беременности и родов у детей сравниваемых групп. Тем не менее отмечается единство в реализации биологических программ роста и развития, а также достоверно низкий уровень соматического и репродуктивного здоровья у матерей, планировавших беременность при помощи ВРТ. Готовится создание доказательного алгоритма, который поможет практикующим докторам и будущим родителям избежать нежелательных последствий и минимизирует риски для жизни и здоровья новорожденных.

Ключевые слова: *вспомогательные репродуктивные технологии, глубоко недоношенные дети, преждевременные роды, бесплодие, летальность новорожденных*

INTRODUCTION

After a short period of increasing birth rates in 2010–2017, a decline began again, associated with the generation born in the 1990s entering childbearing age. Similar trends as in the Russian Federation (RF) emerged in St. Petersburg, which required the adoption of serious government decisions in the area of improving women's and children's health. The President of the Russian Federation and the Government of Russia adopted enhanced measures of social support for those in need under the large-scale projects "Healthcare" and "Demography", which provide for accelerated construction of schools and preschool institutions [12].

At the same time, one of the problems in both the medical and social spheres remains infertility. In the context of a difficult demographic situation, the use of all resources to increase the birth rate becomes an important factor. If there is no effect of treatment for infertility within a year, methods of assisted reproductive technologies (ART) can be offered, which involve not only the onset of pregnancy, but also nursing of babies [9].

Currently, the number of births as a result of ART is increasing and reaches 2,7% (data from the ART registry report of the Russian Association of Human Reproduction (RAHR) for 2021). According to operational data from the Organizational and Methodological Center for Analysis and Forecasting of Maternal and Child Health of the Health Committee of St. Petersburg, the number of children born using ART in 2023 was more than 5%.

According to the data, presented by Christine Wyns on July 5–8, 2020 at the European Society of Human Reproduction and Embryology (ESHRE 2020) Annual Meeting, Russia ranks first in the number of cycles of ART performed (137,211). In previous years, according to RAHR, more than 1,5 million treatment cycles were carried out.

In Russia, the use of ART is regulated by Federal Law No. 323-FZ "On the fundamentals of health protection of citizen of the Russian Federation" (Chapter 6, Article 55) dated November 21, 2011 and orders of the Ministry of Health of the Russian Federation dated August 30, 2012 No. 107n (as amended on February 1, 2018) "On the procedure for the use of assisted reproductive technologies, contraindications and restrictions on their use", as well as "On approval of the standard of medical care for infertility using assisted reproductive technologies" dated October 30, 2012 No. 556n.

Along with the problems of the birth rate, the issue of nursing and rehabilitation of extremely premature babies is no less acute. According to the clinical practice guidelines "Preterm births", published in the letter of the Russian Ministry of Health dated December 17, 2013 No. 15-4/10/2-9480, "the frequency of premature births in developed countries is 5–7%, neonatal mortality is 28%. About 15 million premature babies are born in the world every year. Preterm births (PB) are a complex medical and social problem associated with solving the problems of improving the subsequent quality of life of children born prematurely, and are associated with material and economic costs".

As it is known, the severity of complications associated with prematurity is inversely proportional to the gestational age [14]. The need to prolong pregnancy, as well as improve the care of deeply premature babies at all stages, have determined the need for more careful monitoring of expectant mothers, especially those who are planning pregnancy using ART methods. It has also been established that multiple pregnancies after in vitro fertilization (IVF) are considered a high-risk group for the development of perinatal pathology in the newborn, caused not only by prematu-

rity, but also by the diseases that the mother has and caused infertility [7].

AIM

The aim of the study is to compare, according to certain criteria, the health status of neonates born at early term gestation, after assisted reproductive technologies and during spontaneous pregnancy

MATERIALS AND METHODS

A retrospective, observational, prolonged (at the time of hospitalization) study was conducted of 42 pairs of newborn children born in St. Petersburg and the Leningrad region as a result of spontaneous pregnancy and after the use of ART at a period of 22 weeks 0 days — 27 weeks 6 days inclusive for the period 2018–2022 as a result of singleton or multiple pregnancies (twins). Of these, 11 infants in each group were born at a very early stage (22–24 weeks), 31 children were born at early term gestation (25–27 weeks). All 4 subgroups were compared with each other. The obtained data were analyzed using the IBM SPSS Statistics v.26 statistical program and the WinPepi additional counting program. Categorical variables are presented as absolute values (n) and their sample proportion (%). Quantitative variables are represented either by the mean and its standard deviation (M±SD) or by the median (Me) with the 1st and 3rd quartiles ([Q1; Q3]). To compare the frequency characteristics of qualitative variables, the Fisher's exact test (F) and Pearson's chi-squared test (χ^2) were used; to compare quantitative variables, nonparametric comparison methods the Kruskal–Wallis (KW) or Mann–Whitney (U) were used at the null hypothesis rejection level of $p < 0,05$.

The following criteria of comparison were used in the work: anthropometric data of the child at birth, scales predicting the condition of newborns, somatic diseases of the mother, obstetric history of the mother, blood tests at birth (including an arterial blood gas test), blood oxygen level, treatment carried out both in the maternity hospital and in the hospital, examinations of the infant during hospitalization, diseases of the child at the time of discharge from the hospital, weight upon transfer to the department of neonatal pathology and weight at discharge, outcome. A total of 100 criteria.

Exclusion criteria: babies born to mothers with alcohol or drug abuse; children born through surrogacy, egg or sperm donation (when the donor was not a spouse); infants whose mothers suffered from a severe viral infection during pregnancy (for example, COVID-19); children from mothers with viral hepatitis B, C, HIV; children from multiple pregnancies (triplets); children with hereditary diseases and severe congenital malformations.

RESULTS

In recent years, the problem of preserving the life and health of premature infants with extremely low birth weight (ELBW) has become especially acute in our country due to the improvement of nursing technologies for this category, as well as the introduction of new live birth criteria in the Russian Federation recommended by WHO [13]. The incidence of premature births in the world in recent years has been 9,5%, with 15,000,000 premature babies born annually and, despite the emergence of new technologies, it is not decrea-

Table 1. Quantitative characteristics of the surveyed groups

Таблица 1. Количественные характеристики обследованных групп

Сроки гестации (Gestation period) / Критерии (Criteria)	22–24 нед/wg	25–28 нед/wg	Одноплодная беременность / Singl pregnancy	Многоплодная беременность/ Twin pregnancy	Пол / Sex		Исход / Outcome	
					ж/f	м/m	выписан/ discharged	ЛИ / LO
СБ / SP, n (%)	11 (26,2)	31 (73,8)	19 (45,3)	23 (54,8)	22 (52)	20 (48)	34 (81)	8 (19)
ВРТ / ART, n (%)	11 (26,2)	31 (73,8)	15 (35,7)	27 (64,3)	24 (57)	18 (43)	31 (73,8)	11 (26,2)
Всего / Total, n (%)	22 (26,2)	62 (73,8)	34 (40,5)	50 (59,5)	46 (55)	38 (45)	65 (77,4)	19 (22,6)

Примечание: ВРТ — вспомогательные репродуктивные технологии; ЛИ — летальный исход; СБ — самостоятельная беременность.
Note: ART — assisted reproductive technologies; LO — letal outcome; SP — spontaneous pregnancy.

Table 2. Maternal morbidity

Таблица 2. Заболеваемость матерей

Критерии / Criteria	Тест / Test	p
1. Заболевания репродуктивной сферы / Diseases of the reproductive sphere	χ^2	0,032
2. Заболевания эндокринной системы / Diseases of the endocrine system	F	0,000
3. Заболевания острыми респираторными вирусными инфекциями / Acute respiratory diseases	F	0,036
4. Заболевания органов кровообращения / Diseases of the circulatory system	χ^2	0,313
5. Заболевания органов желудочно-кишечного тракта / Diseases of the gastrointestinal tract	χ^2	0,051
6. Заболевания органов мочевыделительной системы / Diseases of the urinary system	χ^2	0,609
7. Болезни глаз и придаточного аппарата / Diseases of the eye and appendage	χ^2	0,058
8. Заболевания, передающиеся половым путем / Sexually transmitted diseases	χ^2	0,322
9. Заболевания нервной системы / Diseases of the nervous system	χ^2	0,500
10. Гестационный сахарный диабет / Gestational diabetes mellitus	χ^2	0,260

sing [14]. In developed countries, it is increasing, primarily as a result of the use of new reproductive technologies [18]. About 5% of them occur before 28 weeks [16].

Perm scientists have found that every third child born as a result of assisted medical technologies is premature (32%). The main factors influencing the birth of a preterm infant in IVF pregnancies are: maternal age over 35 years, duration of infertility and a history of miscarriage [5].

When assessing the development and condition of babies born as a result of the use of ART, some contradictions have arisen. Until now, experts of different medical specialties (embryologists, neonatologists, psychologists) have not come to a consensus regarding the prediction of health and quality of life of this group of children.

Due to the fact that, as a rule, ART is performed in centers that are separated from the antenatal clinic where the woman is subsequently observed, healthcare facilities where the delivery occurs, and clinics where children are observed in the coming years, and also the fact that 63% of parents conceal the method of pregnancy, it is practically impossible in the Russian Federation to obtain reliable information about the health of children born after ART [8].

In connection with the ambiguity of estimates of the health and development of children conceived by ART and usually carried out without strict parallel control, certain doubts arise about the equivalence of biological processes in naturally conceived babies and children conceived through ART.

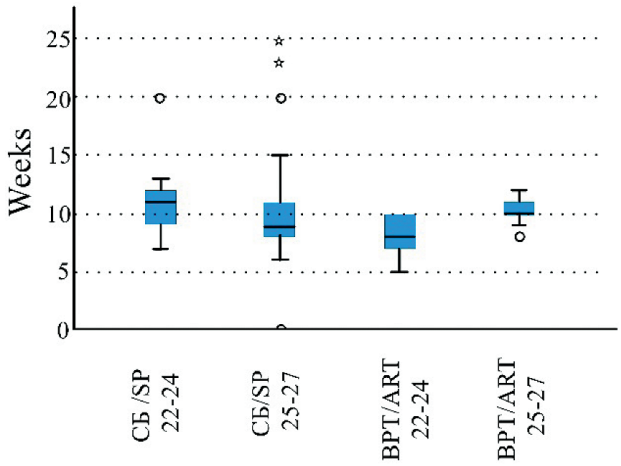

Fig. 1. Registration in the women's consultation

Рис. 1. Постановка на учет в женскую консультацию

The scientific work plans to show the importance of assessing children's development using the randomization method, namely, distribution by development conditions (pairwise selection, the "copy-pair" method) in order to minimize differences in the pre-, intra-, and postnatal periods of development of infants born in the early stages of gestation.

Table 1 presents the design of the study. Children were selected using the "copy-pair" method by gestation period, place of birth and nursing (St. Petersburg and the Leningrad Region), maximally matched by sex and number of fetuses (single or twin pregnancy).

Initially, ART methods were used to overcome reproductive problems associated with obstruction or absence of fallopian tubes. Currently, the

Table 3. Comparative anthropometry data with glow

Таблица 3. Сравнительные данные антропометрии при рождении

Критерии / Criteria	Масса / Weight		Рост / Height		Окружность головы / Circle heads		Окружность груди / Circle breast	
	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART	СБ / SP	ВРТ / ART
M (±SD)	792±145	746±145	531±2	31±3	23±4	23±2	21±2	21±2
Me	790	750	31	32	23	23	21	21
[Q1; Q3]	[680; 900]	[670; 860]	[30; 33]	[29; 33]	[22; 25]	[22; 25]	[22; 25]	[19; 22]
U/P	745/0,220		555,5/0,975		842,0/0,861		818,0/0,833	

Примечание: ВРТ — вспомогательные репродуктивные технологии; СБ — самостоятельная беременность (здесь и далее в таблицах).
Note: ART — assisted reproductive technologies; SP — spontaneous pregnancy (here and further in the tables).

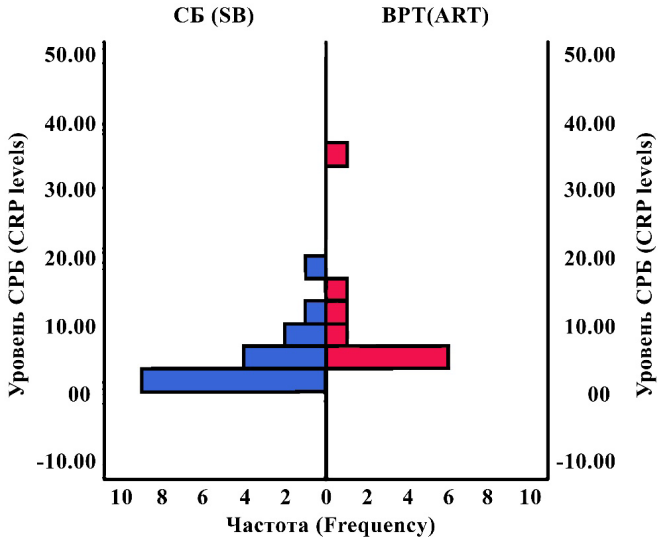

Fig. 2. Comparison of C-reactive (CRP) protein levels in newborns with assisted reproductive technologies (ART) and spontaneous pregnancy (SP)

Рис. 2. Сравнение уровня С-реактивного белка (СРБ) у новорожденных при вспомогательных репродуктивных технологиях (ВРТ) и самостоятельной беременности (СБ)

indications for the use of these methods are much broader and include various causes of infertility: endocrine, idiopathic, male factor, etc. However, the maternal health is extremely important for the future child. Most women who have resorted to ART are in the high-risk group for complicated pregnancy and childbirth, which adversely affects the intrauterine development of the fetus [17]. The health status of mothers undergoing ART and mothers who became become pregnant naturally at the time of conception and during pregnancy differ; the results are shown in Table 2.

According to the data in Table 2, diseases of the endocrine system, reproductive sphere and acute respiratory diseases are higher in mothers whose babies were born through ART. The total number of diseases in mothers in the ART group is also higher (p=0,032). Antibiotic therapy was used significantly more often in pregnant women after ART (p=0,004).

According to the chart (Fig. 1), mothers whose children were born using ART at an extremely early stage were registered with antenatal clinics earlier than others (p=0,019).

Modern studies devoted to the evaluation of long-term results are ambiguous and often contradictory. Most studies do not show significant differences between infants depending on the method of conception [8, 21]. At the same time, the need for a more in-depth study of this issue is recognized, and it is also important to research the general functioning of the family system in the case of ART before making final conclusions [22].

The study did not reveal reliable differences in the assessment of anthropometric data in newborns in the comparison groups. The Apgar scores of neonates born early term gestation in the compared groups did not reveal reliable differences (p> 0,05 at all stages of assessing the condition

of newborns; Apgar1 p = 0,225; Apgar2 p = 0,418; Apgar3 p = 0,507).

The prenatal period can be used to judge both the effectiveness of ART and the adequacy of fetal development. Factors influencing pregnancy outcome include the use of stimulating hormones, changes in hormone levels, temporary presence of gametes outside the woman's body, the frequency of in vitro fertilization (IVF) and the woman's somatic condition, the impact of environmental factors on the mother and fetus during intrauterine development, methods of delivery and social factors [10].

Some authors claim that the use of ART increases the miscarriage rates, which may affect the further development of children [1, 3].

According to the research conducted by G.U. Asymbekova et al. (2014), in the group of women with ART, it was more common to resort to operative delivery, since the probability of diseases and the risk of complications are higher for them than for women with spontaneous pregnancy [2]. The author's work also obtained data showing that operative delivery at an early stage of gestation is significantly more often used for mothers after ART (p = 0,024).

Table 4. Treatment in the early postnatal period

Таблица 4. Лечение в раннем постнатальном периоде

Критерии / Criteria	СБ / SP Me [Q1; Q3]	ВРТ / ART Me [Q1; Q3]	Тест	P
1. Искусственная вентиляция легких (дни) / Mechanical ventilation (days)	23 [7; 38]	20 [8; 39]	U=613,000	0,854
2. Кислородная зависимость (дни) / Oxygen dependency (days)	69 [59; 90]	78[57; 94]	U=593,000	0,529
3. Переход на полное энтеральное питание (дни) / Transition to full enteral nutrition (days)	49 [24; 83]	45 [23; 70]	U=439,000	0,440
4. FiO_2 max роддом / FiO_2 max maternity hospital	0,60 [0,40; 0,80]	0,50 [0,40; 0,70]	U=749,500	0,232
5. FiO_2 min роддом / FiO2 min maternity hospital	0,25 [0,21; 0,30]	0,25 [0,21; 0,30]	U=838,500	0,685
6. FiO_2 в стационаре / FiO_2 in the hospital	0,34 [0,30; 0,45]	0,35 [0,30; 0,45]	U=909,500	0,655
7. Сурфактант (количество) / Surfactant (quantity)	1 [1; 2]	2 [1; 2]	U=950,500	0,496

Критерии / Criteria	Количество человек / Number of people n (%)	Количество человек / Number of people n (%)	Тест	p
1. Инотропная терапия (адреналин) / Inotropic therapy (adrenaline)	13 (31%)	13 (31%)	χ^2=0,000	0,593
2. Инотропная терапия (дофамин) / Inotropic therapy (dopamine)	20(47,6%)	14(33,3%)	χ^2=1,779	0,133
3. Инотропная терапия (добутамин) / Inotropic therapy (dobutamine)	34(81%)	34(81%)	χ^2=0,000	0,609
4. Гормональная терапия / Hormone therapy	26(61,9%)	20(47,6%)	χ^2=1,730	0,136
5. Противосудорожная терапия / Anticonvulsant therapy	5(12,2%)	3(7,3%)	χ^2=0,554	0,356
6. Обезболивание (фентанил) / Anesthesia (fentanyl)	20(47,6%)	16(38,1)	χ^2=0,778	0,254
7. Атибактериальная терапия / Antibacterial therapy	42(100%)	42(100%)	Не применимо / Not applicable	Не применимо / Not applicable

Table 5. Pairwise comparison of mortality of children born in the early stages during ART and from independent pregnancy

Таблица 5. Попарное сравнение летальности детей, рожденных на ранних сроках при ВРТ и от самостоятельной беременности

Общий фактор / Common factor χ^2		СБ / SP (22–24)		СБ / SP (25–27)		ВРТ / ART (22–24)		ВРТ / ART (25–27)	
		p	χ^2	p	χ^2	p	χ^2	P	
Сроки гестации (нед) / Gestation period (weeks of gestation)	СБ / SP (22–24)			0,004	0,949	2,959	0,085	0,170	0,680
	СБ / SP (25–27)	0,004	0,949			6,002	0,014	0,465	0,495
	ВРТ / ART (22–24)	2,959	0,085	6,002	0,014			8,912	0,003
	ВРТ / ART (25–27)	0,170	0,680	0,465	0,495	8,912	0,003		

However, it is known that the risk of infectious complications during operative delivery is 2,8 times higher compared to vaginal delivery [22]. Numerous scientific studies demonstrate that children born as a result of operative delivery, have an increased risk of allergic and autoimmune diseases, type 1 diabetes mellitus and obesity in the future, which dictates the obstetrician-gynecologist to take a more rational approach to the choice of the method of delivery [20, 21].

C-reactive protein (CRP) level in children born through ART is shown in Fig. 2, which indicates a more pronounced inflammatory process in children born after ART (p=0,04). Other blood parameters in this study did not reveal any significant difference.

Table 4 shows that there is no significant difference in the management of children born at an early stage of gestation in a maternity hospital and in the intensive care unit of a hospital. The treatment methods used corresponded to the recommendations for the care of newborns with respiratory distress syndrome [4].

Despite the fact that mothers of children born through ART were registered at antenatal clinics at a reliably early period, the mortality rate of these newborns is higher than in the other groups p=0,003 (Table 5).

In this work, no significant differences were found in anthropometric data or in the tactics of managing children in the study groups and those born at early term gestation. In the maternity hospital and intensive care unit of the hospital, treatment was consistent with clinical practice guidelines for management extremely low birth weight infants, as well as with protocols for providing medical care to this category of neonates. However, further in-depth research is required to identify the causes of perinatal mortality in children born at a very early stage (22–24 weeks), p=0,003 (Table 5) after the use of ART, taking into account their significant early registration at antenatal clinics.

DISCUSSION

The conducted research revealed a number of organizational factors that substantially complicated the work. Firstly, the lack of special document labeling of pregnant women and children born using ART entailed significant searches: doses of estrogens, the number of cycles of maintenance therapy, etc. This was accompanied by negativism of mothers who did not want to communicate on infertility and the methods of its treatment that were used in each particular case.

The data from the performed work showed unity in the implementation of biological programs of growth and development, as well as a significantly lower level of somatic and reproductive health in mothers who planned pregnancy using ART. In addition, the pregnancy of expectant mothers more often occurred against the background of infectious diseases, which required the appointment, possibly due to greater immunodeficiency, of antibacterial therapy.

The high CRP level in children of the ART group at birth (p = 0,040) to a certain extent confirms the presence of intrauterine infection [11]. Delivery of women in this group was carried out surgically (p = 06024), since the probability of diseases and high risk of complications in them is higher than in women with spontaneous pregnancy [15].

Treatment of newborns at the stage of the maternity hospital and intensive care unit did not differ significantly. At the same time, children born after ART at a very early gestational age (22–24 weeks) died significantly more often, which is most likely a reliable sign in favor of reduced adaptive capacities in babies conceived by ART. Almost all of the deceased were diagnosed with intrauterine infection.

In order to reduce the risk of adverse perinatal outcomes, it is necessary to structure obstetric-gynecological, neonatal and pediatric counseling in families planning ART at the outpatient stage [8].

CONCLUSION

Thus, based on the conducted study, it can be noted that the course of pregnancy and childbirth in infants of the comparison groups is ambiguous. Extremely premature babies are at high risk of infectious complications, which sharply reduces their adaptive capacities. Modern studies are unanimous in their opinion about the predominantly ascending route of infection in case of intra-amniotic infection [6]. Obstetric problems associated with ART are primarily due to the age of the mother, the presence of extragenital pathology. The most significant risk is multiple pregnancy, which should be avoided, since in this case the situation can become difficult to manage [19]. The high risk of death or development of complications will apparently require new recommendations for pregnancy registration, its management and providing medical care to newborns. A logical and relevant solution to the problem may be the creation of ART registries [23].

These results showed only some differences between the groups of children. In order to identify risk groups and determine the correct medical tactics, it is planned to create an evidence-based algorithm that will help practicing doctors and future parents avoid undesirable consequences and minimize the risks to the life and health of newborns.

ADDITIONAL INFORMATION

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Вклад авторов. Автор лично внес вклад в разработку концепции, проведение исследования и подготовку статьи, прочел и одобрил финальную версию перед публикацией.

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A CLINICAL CASE OF A CHILD WITH TYPE I DIABETES MELLITUS WITH THE SUBSEQUENT DEVELOPMENT OF ENCEPHALOPATHY

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Abstract. The aim of the work was to review a clinical case of a child with type 1 diabetes mellitus (DM1) with severe cognitive impairment due to the development of diabetic encephalopathy. The analysis of the preceding factors of the manifestation of DM1 in a child is carried out, as a result of which, against the background of prolonged hyperglycemia and insulin deficiency, there was an increase in metabolic acidosis with a subsequent complication in the form of diabetic encephalopathy (DE). Subsequent metabolic and hypoxic changes in the child's body led to a decrease in cognitive functions.DE is a characteristic complication of DM1 in children, since its development is mainly due to ineffective metabolic control, as well as incorrectly selected therapy. An assessment of anthropometric data, as well as laboratory parameters, was carried out before and after adjusting the treatment of DM1.

Keywords*: type 1 diabetes mellitus (DM1), diabetic encephalopathy (DE), diabetic coma, metabolic acidosis treatment of DM1, children*

КЛИНИЧЕСКИЙ СЛУЧАЙ РЕБЕНКА С САХАРНЫМ ДИАБЕТОМ 1-го ТИПА С ПОСЛЕДУЮЩИМ РАЗВИТИЕМ ЭНЦЕФАЛОПАТИИ

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Резюме. Цель работы — обзор клинического случая ребенка с сахарным диабетом 1-го типа (СД1) с выраженным нарушением когнитивных способностей из-за развития диабетической энцефалопатии. Проведен анализ предшествующих факторов манифестации СД1 у ребенка, вследствие которых на фоне длительно протекавшей гипергликемии и дефицита инсулина случился метаболический ацидоз с последующим осложнением в виде диабетической энцефалопатии (ДЭ). Дальнейшие метаболические и гипоксические изменения в организме ребенка привели к снижению когнитивных функций. ДЭ является характерным осложнением СД1 у детей, поскольку ее развитие обусловлено преимущественно неэффективным метаболическим контролем, а также некорректно подобранной терапией. Была проведена оценка антропометрических данных и лабораторных показателей до и после корректировки лечения СД1.

Ключевые слова: *сахарный диабет 1-го типа, диабетическая энцефалопатия (ДЭ), диабетическая кома, метаболический ацидоз, дети*

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INTRODUCTION

In recent years, the morbidity of diabetes mellitus has increased significantly in developed countries with high economic growth. In a number of countries, there is a disproportionately high increase in the incidence of type 1 diabetes mellitus (DM1) in children under 5 years of age. According to the International Diabetes Federation (IDF) for 2021, the total number of children and adolescents (under 19 years) with DM1 in the world is more than 1,2 million people, of which more than half (54%) are children under 15 years of age. The morbidity of DM1 is increasing every year. Annually, more than 108 thousand children aged 0 — 14 years and more than 41 thousand adolescents aged 15 — 19 years fall ill [3, 4, 12].

In most countries, the onset of DM1 develops in up to 90% of cases, most often in childhood, while among older age groups the prevalence of DM1 is from 5 to 10% [3, 4, 6]. The peak incidence occurs during the period of early puberty and is detected in girls 1–2 years earlier than in boys. By the end of puberty, the morbidity decreases for children of both sexes [8, 17].

DM1 is accompanied by complications of the kidneys, retina, peripheral nervous system and blood vessels. Recently, diabetic complications of the central nervous system (CNS) have been studied more closely. There is no generally accepted definition of diabetic encephalopathy (DE), but it does not include cerebral edema that develops during ketoacidosis or hypoglycemia.

Clinically, DE manifests itself as neurosis-like disorders and psychotic-like experiences, organic, neurological and autonomic clinical presentation [8]. It includes characteristic biochemical, electrophysiological and morphological changes that can lead to cognitive impairment and significantly reduce the quality of life of both the patient and his relatives [3, 10, 16].

DE in its pure form occurs only in patients with DM1 (in 80% of cases) since its development is mainly due to ineffective metabolic control [3, 4].

According to epidemiological data, the onset of diabetes mellitus at an early age has a major negative impact on the developing brain. The application of single-photon emission computed tomography has shown a reduction in cerebral blood flow in the frontal lobe areas and in the basal ganglia. Chronic hyperglycemia is associated with a decrease in neurophysiological test results and structural changes [4, 5].

ENCEPHALOPATHY IN TYPE I DIABETES MELLITUS

Recently, there has been increasing evidence of adverse effects of DM1 on the CNS and cognitive functions. Studies of children with DM1 have shown impairments in attention, processing speed, executive functions, intelligence and memory [5, 7, 14].

The mechanism underlying DE in DM1 is multifactorial and is still far from being fully understood (Fig. 1). It is assumed that insulin deficiency and its impact on other neurotrophic factors play an important role in mediating the effects of neurotransmitters and ensuring interneuronal interactions. Concomitant oxidative stress and activation of apoptosis may be associated with hyperglycemia, but perhaps to a greater extent with impaired insulin signaling, which can be corrected by C-peptide and intranasal administration of insulin [1, 4]. All disorders over time lead to neuronal cell loss and disintegration of neuronal networks that are the basis of cognitive function.

White matter atrophy associated with hyperactivation of receptors for advanced glycation end products is revealed [8, 10, 13].

The mechanism of cells and tissue damage by endogenous and exogenous AGEs (advanced glycation end products) is as follows:

1) activation of receptor-mediated signaling pathways leading to oxidative stress, inflammation and gene expression modulation;
2) changes in the structure and function of stable long-lived proteins, in particular connective tissue proteins due to irreversible cross-linking with AGEs;
3) glycation of intracellular proteins and lipids leads to disruption of cellular function [2, 9, 11].

White matter changes relate to decreased expression of myelin protein, oligodendrocyte loss, and are associated with increased astrogliosis, which is accompanied by increased expression of receptors for advanced glycation end products, tumor necrosis factor-alpha and interleukin-6 in the white matter [2].

Absolute insulin deficiency leads to decreased utilization of glucose by insulin-dependent tissues. Hyperglycemia develops in the blood, and severe energy "starvation" occurs in the tissues. This contributes to a sharp increase in the level of all insulin-counteracting hormones in the blood (glucagon, catecholamines, cortisol, adrenocorti-

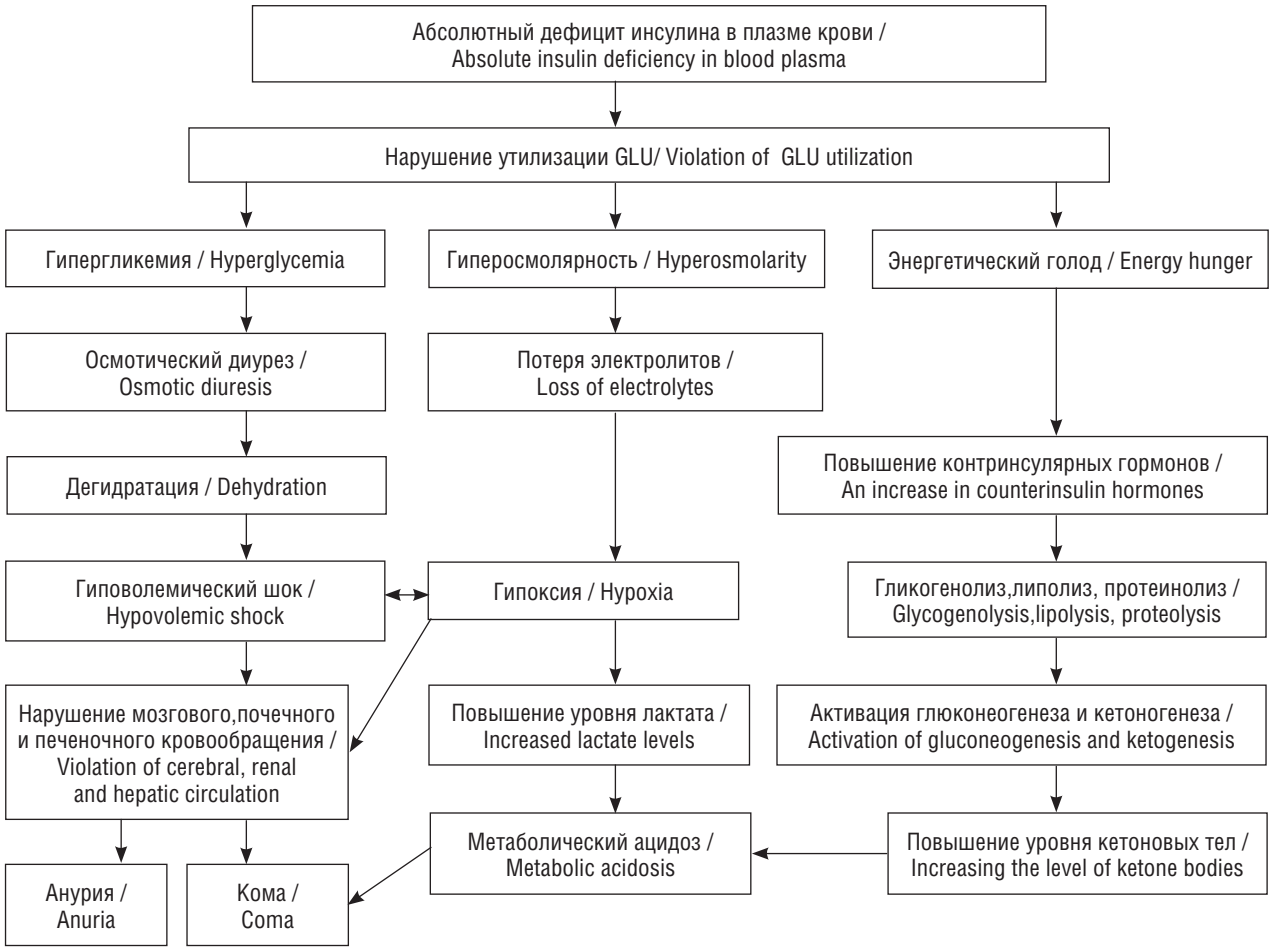

Fig. 1. The mechanism of development of diabetic encephalopathy in DM1

Рис. 1. Механизм развития диабетической энцефалопатии при СД1

cotropic hormone (ACTH), somatotropic hormone (STH)). In the body, lipolysis, glycolysis and proteolysis are activated, which leads to the formation of substrates for gluconeogenesis in the liver and kidneys. Gluconeogenesis in combination with impaired glucose utilization by tissues is the most important cause of rapidly increasing hyperglycemia, the increase in plasma osmolarity, intracellular dehydration, and osmotic diuresis [10, 11, 13].

In turn, activation of lipolysis leads to the liver not using fatty acids for triglyceride synthesis. As a result, some fatty acids are included in beta oxidation and ketogenesis. Ketone body synthesis occurs from amino acids such as isoleucine, leucine and valine, which accumulate as a result of excessive proteolysis. Accumulation of acetyl-CoA, acetoacetate and beta-hydroxybutyrate leads to depletion of alkali reserve in the blood and the development of metabolic acidosis. Synthesis of ketones by the body is higher than their consumption and utilization during excretion in urine, which also leads to metabolic acidosis (diabetic coma) [15].

Proteolysis disrupts the nitrogen balance and azotemia develops. Intracellular dehydration is replaced first by extracellular and then by general dehydration of the body. There is a reduction in tissue and renal blood flow, a deficiency of electrolytes Na^+, K^+, Cl^- is observed. Dehydration leads to hypovolemia, which is the cause of a reduction in cerebral, renal and peripheral blood flow. This intensified the already existing hypoxia in CNS and peripheral tissues. Tissue hypoxia promotes in these tissues the activation of anaerobic glycolysis and the accumulation of lactic acid, which can cause lactic acidosis [10, 11, 17].

Thus, the severity of the patient's condition is due to active dehydration of the body, decompensated metabolic acidosis, electrolyte deficiency, hypoxia, hyperosmolarity and can be complicated by diabetic encephalopathy and, in serious cases, coma [1, 4, 8].

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The pathogenesis of DE is associated with two main types of disorders: metabolic and hypoxic. The development of microangiopathy is mediated by the accumulation of low-density lipoproteins (LDL) in the blood vessel wall, activation of lipid peroxidation (LPO) processes, increased formation of free radicals, and suppression of the synthesis of prostacyclin, which has an antiplatelet and vasodilatory effect. The progression of microangiopathy leads to a reduction in endoneurial blood flow with the development of hypoxia, which contributes to the switching of the energy metabolism of the nervous tissue to ineffective anaerobic glycolysis, during which only two molecules of adenosine triphosphate (ATP) are formed from one molecule of glucose, while in the reaction of aerobic glycolysis — 38 molecules. As a result, the concentration of phosphocreatinine in neurons decreases, the lactate content increases, which leads to the development of oxygen and energy starvation of the nervous tissue. The reduction in endoneurial microcirculation and aggravation of nerve fiber function disorders contribute to a decrease in production and an increase in destruction of nitric oxide (NO), which has a vasodilatory effect, which can become one of the causes of the development of arterial spasm, that is an important pathogenetic mechanism for the development of arterial hypertension in diabetes mellitus [3, 4, 8, 10, 11]. In addition to the pathogenetic significance of endoneurial blood flow disturbances, metabolic disorders also play an important role. It has been established that the decrease in the impulse conduction velocity in myelinated nerve fibers is caused by a pathologically high intra-axonal concentration of Na^+ ions, in the development of which the main role belongs to a decreased Na^+/K^+-ATPase activity, which causes secondary vascular diseases, neurotrophic disorders, neurotoxicosis and, as a consequence, structural changes in neurons, as well as a violation of nerve conduction velocity. Diabetes mellitus has a huge impact on the white matter loss of the brain [8, 13, 15].

CLINICAL CASE

A girl, 5 years 7 months old, was admitted to the emergency department in clinic of the hospital No. 1 with classic symptoms of diabetes mellitus and ketoacidosis, as well as complaints of weakness and sluggishness. Due to the untimely seeking medical help, the patient's condition upon admission was extremely serious. Laboratory data: hyperglycemia (25 mmol/l), ketoacidosis, increased glycated hemoglobin, glucosuria. On the third day, against the background of the administration of high doses of insulin, clinical death was recorded due to a sharp fall in blood glucose levels with the subsequent formation of brain herniation. A nasogastric tube was inserted into the patient. On the 4th day from the onset of the disease, the girl was transferred to the clinic of hospital No. 2 in extremely serious condition. The level of disorders of consciousness: grade II deep coma. Early anamnesis without features. The patient was not registered with medical specialists. A brain magnetic resonance imaging (MRI) was performed: signs of hypoxic-ischemic encephalopathy in the form of diffuse edema in the white matter of the brain, ischemic/necrotic changes in the basal ganglia on both sides, multifocal cortical laminar necrosis. Expansion of the external and internal cerebrospinal fluid spaces. According to the results of multispiral computed tomography of the brain, atrophic changes in the brain and diffuse ischemia were observed. Triventricular hydrocephalus was noted.

Three months later, the patient was transferred to hospital 3 with the diagnosis: mixed encephalopathy, organic brain injury of mixed genesis (hypoxic-metabolic), decerebrate rigidity, structural metabolic epilepsy, type 1 diabetes mellitus, severe protein-energy malnutrition.

Comprehensive drug treatment was carried out, which included intensive insulin therapy (levemir, novorapid), anticonvulsants (keppra) and antiepileptic (clonazepam, convulex) drugs, muscle relaxants (baclosan), anxiolytics (relanium), carminatives (espumisan baby), enzymes (creon), a strict diet using nutrient mixtures (clinutren+Hipp HA1).

Against the background of a properly selected diet and drug treatment, positive dynamics were noted in leveling the correlation between the expected and obtained results of BMI from 11,75 to 14,49 (Fig. 2); the child's weight from 15 to 19,5 kg (Fig. 3, a, b), fat mass from 2,28 to 3,23 kg (Fig. 4); fat-free mass from 12,72 to 14,21 kg (Fig. 5), total water from 9,31 to 10,4 l (Fig. 6), basic exchange from 982 to 1031 kcal (Fig. 7).

During the treatment, an increase in glucose levels was periodically noted, which was stopped by timely administration of insulin in an appropriate dose (Fig. 8).

By the age of 5 years and 10 months, positive dynamics in the patient's physical development were revealed: she grew by 3 cm, gained 4,5 kg of body mass. A decrease in body fat mass and a compensatory increase in basic exchange were noted.

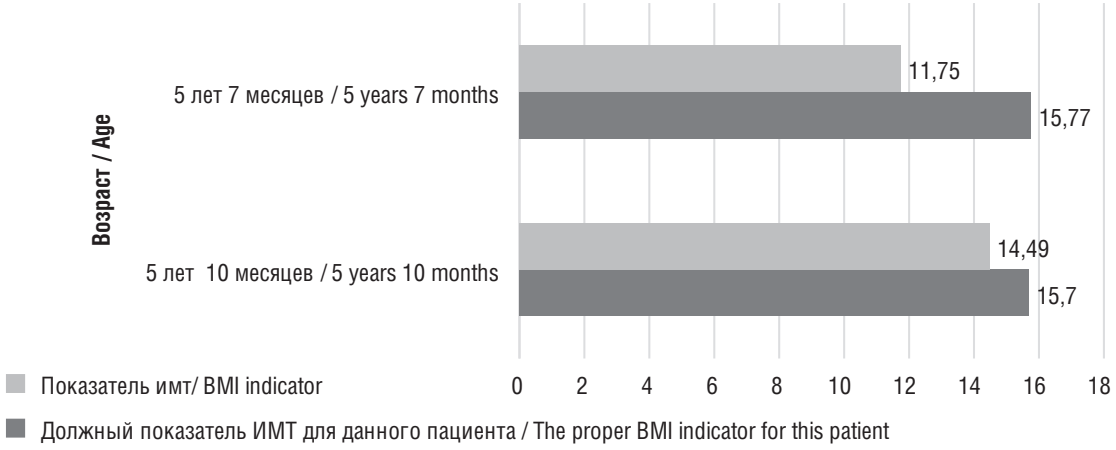
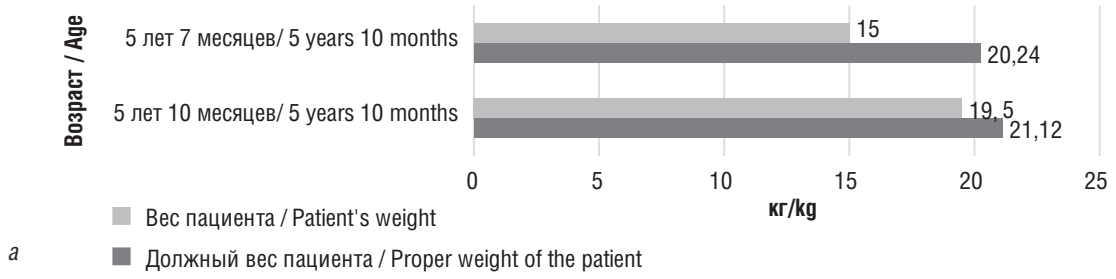


Рис. 2. График соотношения имеющегося индекса массы тела с должным

Fig. 2. A graph of the ratio of the available body mass index to the proper one



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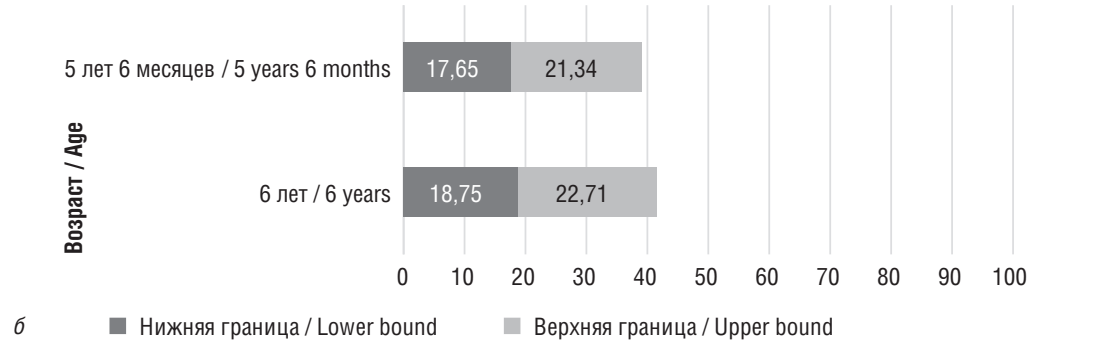

б

Fig. 3. Graph of weight dynamics (*a*), A graph of the patient's body weight compared to the norm corresponding to a given age (*b*)

Рис. 3. График динамики массы (*а*), график массы тела пациента в сравнению с нормой, соответствующей данному возрасту (*б*)

The girl could independently swallow pureed food, suck from a bottle, and her mother sometimes gave her additional water from a cup. The child was discharged from the hospital with recommendations under the supervision of a pediatric endocrinologist at her place of residence.

CONCLUSION

The uniqueness of this case is that it is necessary to take into account the possible acute development of DE at the onset of the disease. In this regard, an individual approach to the treatment of such children is needed in a specialized hospital under the supervision of a group of medical specialists (endocrinologist, gastroenterologist, neurologist, nutritionist). Probably, the most effective treatment of diabetes mellitus in these conditions is the installation of an insulin pump and non-invasive devices for monitoring blood glycemia. The success of therapy also depends on the patient's

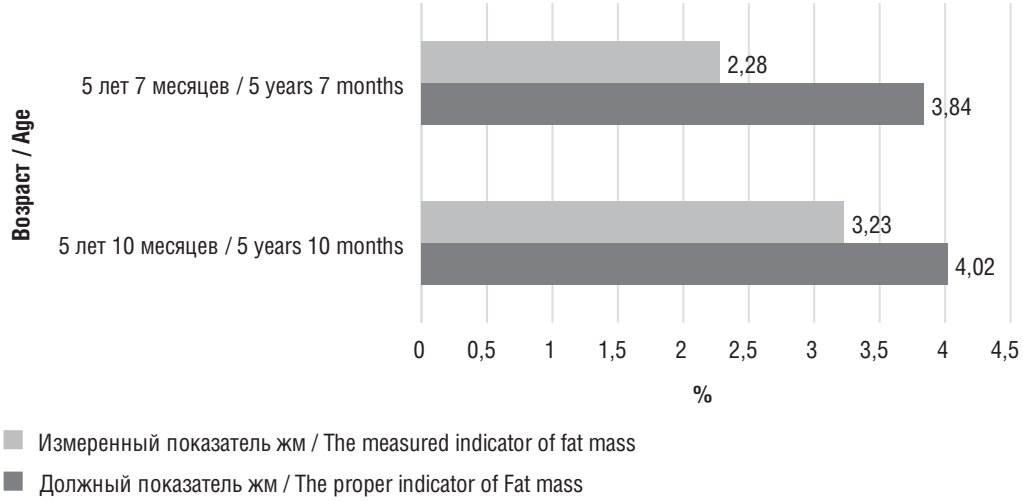

Fig. 4. A graph of the dynamics of fat mass

Рис. 4. График динамики жировой массы

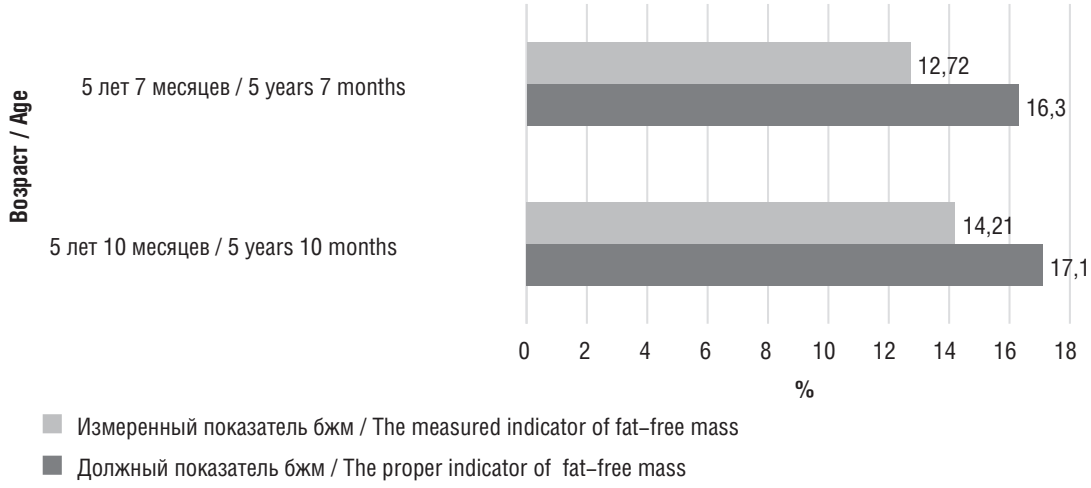

Fig. 5. Graph of the dynamics of fat-free mass

Рис. 5. График динамики безжировой массы

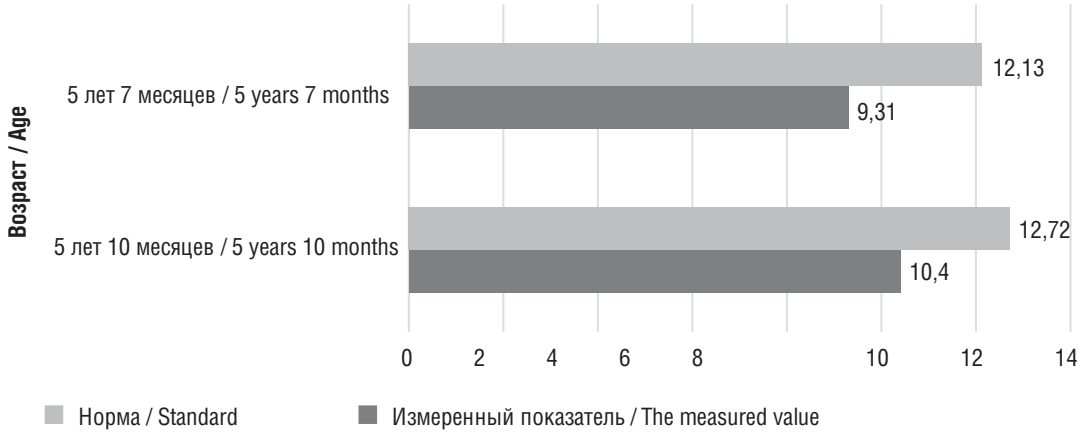

Fig. 6. A graph of the ratio of the amount of total water in the norm and in this patient

Рис. 6. График соотношения количества общей воды в норме и у данного пациента

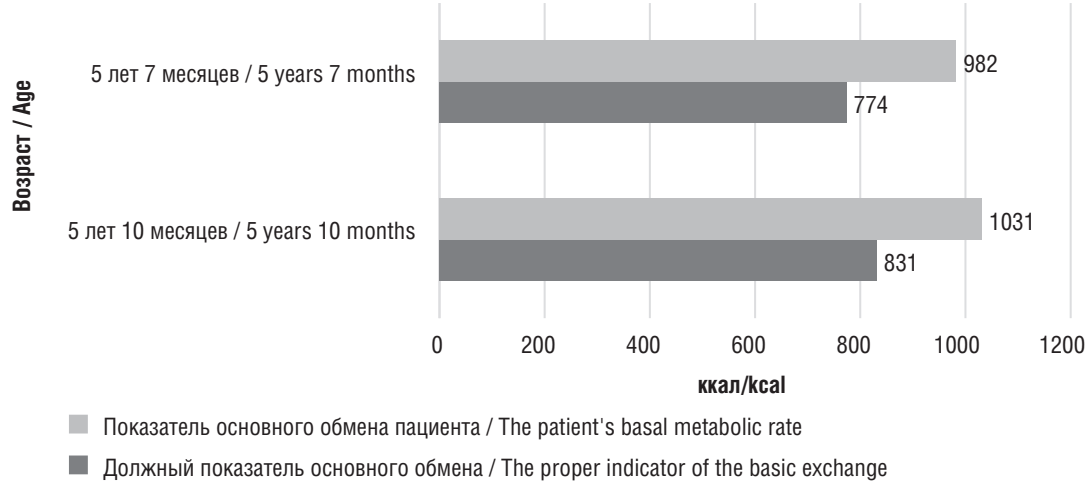

Fig. 7. The dynamics of changes in the basic exchange

Рис. 7. Динамика изменений основного обмена

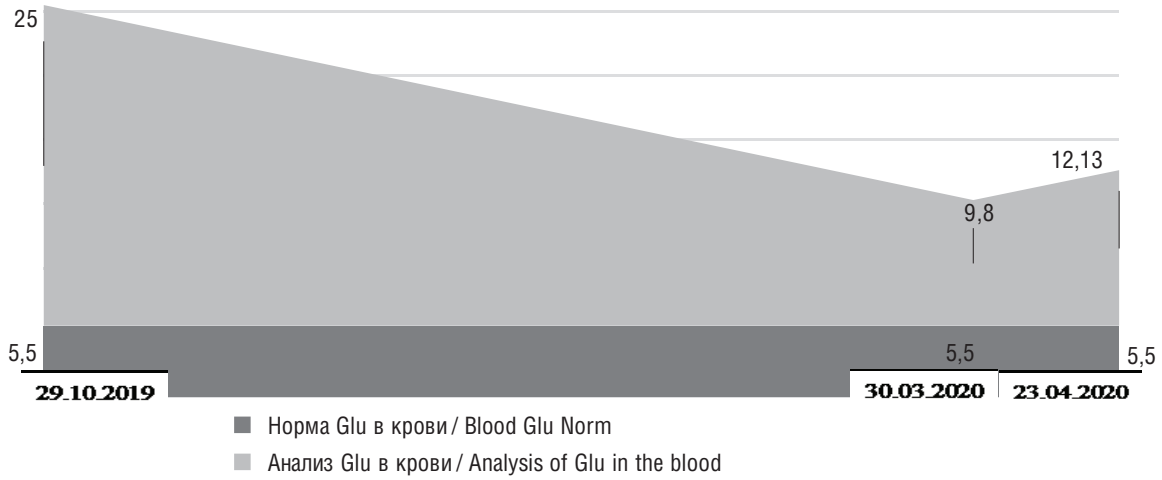

Fig. 8. Dynamics of changes in the concentration of GLU in the blood

Рис. 8. Динамика изменения концентрации GLU в крови

nutrition, which can be ensured by insertion a gastrostomy. The child's parents should be clearly informed about the correct gastrostomy care.

ADDITIONAL INFORMATION

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

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие законных представителей пациента на публикацию медицинских данных.

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FOR THE ANNIVERSARY OF PROFESSOR VALENTINA IVANOVNA GUZEVA

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К ЮБИЛЕЮ ПРОФЕССОРА ГУЗЕВОЙ ВАЛЕНТИНЫ ИВАНОВНЫ

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Valentina Ivanovna Guzeva (Ivanova) was born on April 15, 1944 — the year of the Great Patriotic War, when the victory of our people over fascists was no longer in doubt, in the Russian village Klyuchishchi, Knyagininsky District, Gorky Region. Her father, Ivanov Ivan Ivanovich, fought against fascists until he was seriously wounded and recognized as a disabled person of the Great Patriotic War. Her mother, Ivanova Lidiya Ivanovna, as a home front worker, gave all her strength for our victory. There were three more younger children in the family. As the eldest, Valentina Ivanovna took on many responsibilities for the younger children — she made sure that they were dressed and shod, fed on time, and did not hurt each other.

After the birth of the children, the family moved to Pavlovsk, a suburb of Leningrad, father worked as a foreman at a construction site, mother worked two, and sometimes three jobs at once. Over time, the family was provided with a comfortable three-room apartment in Pavlovsk, and all the children studied well at the Pavlovsk school.

Responsibility for younger children taught Valentina Ivanovna to be sociable, independent and make responsible decisions. And so, after finishing school, without consulting anyone, she decided to become a pediatrician and submitted documents to the admissions committee of the Leningrad Pediatric Medical Institute (LPMI), where, after successfully passing the entrance exams, she was enrolled in the first year of the pediatric faculty.

In order to make it to classes, she had to get up early, take the commuter train to Vitebsk Station in any weather, and get to the institute by public transport. At the institute, as at school, she had many friends, she was interested in social and scientific work, but was especially fond of music and loved to sing — at some point she even thought about becoming a singer. However, she did not change her future profession and in 1967 successfully graduated from the university, receiving a medical degree in the specialty "Pediatrics".

In those years, graduates of higher educational institutions were assigned to work according to the orders of the relevant ministry. Valentina Ivanovna could have received a job referral in Leningrad or Pavlovsk, but she preferred the position of a pediatrician at the Staritskaya Central District Hospital. There, she quickly earned the respect of the hospital staff and local residents. To this day, Valentina Ivanovna maintains good relations with her former colleagues, and many of them in Staritsa remember her with kind words. Several years ago, already being chief freelance children's specialist of the Ministry of health of Russia in the specialty "Neurology", she visited the Staritskaya Hospital where she was warmly welcomed by the current chief medical officer and hospital staff.

The frameworks of the doctor's practical work no longer satisfied Valentina Ivanovna, she wanted to expand her scientific and practical knowledge, and this could only be done in the leading pediatric training and research center. That is why, after three years of work at the Staritskaya hospital, Valentina Ivanovna asked the hospital management to fire her in order to move to Leningrad. They met her halfway, although it is not every day that you meet doctors who, in 3 years of work, have earned the gratitude from the Minister of Health of the RSFSR himself with the wording "For many years of good work in organizing and providing medical and preventive care to the population, I express my gratitude."

At LPMI, Valentina Ivanovna was first accepted to the Clinical Hospital of the Institute as a doctor of the children's emergency department (1970), in 1971 she was transferred to the position of senior laboratory assistant of the Department of Nervous Diseases, in 1973 — to the position of doctor of the Clinic for Nervous Diseases, and in 1978 she was elected by competition to the position of assistant of the Department of Nervous Diseases.

In 1979, Valentina Ivanovna married a teacher of technical university and changed her last name to Guzeva. Victoria, her first daughter was born in 1982, and a daughter Oksana was born in 1983. At the same time, Valentina Ivanovna did not interrupt her scientific and pedagogical activities with parental leave, and frequently had lack of sleep, working even at night. Both daughters graduated from the pediatric university, became neurologists, defended doctoral theses and have the title of professor. Husband, Valentin Vasilyevich Guzev is a Doctor of technical sciences, Professor.

At the Department, Valentina Ivanovna performs not only medical and teaching duties, but also conducts a large research work in the field of child neurology. As the result she published in 1983 the dissertation "Epileptic and non-epileptic paroxysms in young children (clinic, diagnosis and treatment)", submitted for the degree of Candidate of Medical Sciences in the specialty "Nervous diseases". After successfully defending her thesis, Valentina Ivanovna publishes about 30 scientific and methodological papers devoted to the development and improvement of diagnostic methods and therapy for patients with severe neurological diseases, provides medical assistance and counselling to sick children and their parents, and is actively engaged in scientific work with students within the framework of the student scientific society.

In 1991, Valentina Ivanovna submitted her thesis "Paroxysmal disorders of consciousness in young children (diagnosis and rehabilitation)" for the academic degree of Doctor of Medical Sciences in the specialties of "Pediatrics" and "Nervous diseases", and in 1992 she was approved for the academic degree of Doctor of Medical Sciences.

In 1993, she was awarded the academic title of Associate Professor, and in 1994 — the academic title of Professor in the Department of Nervous Diseases and Neurosurgery.

In 1993, Valentina Ivanovna was elected head of the Department of Nervous Diseases and Neurosurgery, and in 1994 she was appointed vice-rector for educational and scientific work of the St. Petersburg State Pediatric Medical University (SPbSPMU). Despite the high administrative workload, Valentina Ivanovna continued to carry out teaching and scientific research in the field of pediatric neurology. During the period 1993–1994, she published about 160 scientific and educational and methodical works, supervised interns and postgraduate students.

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Despite the high administrative workload, Valentina Ivanovna continued to carry pedagogical load and scientific research in the field of childhood neuroscience. Between 1993 and 1994, she published about 160 scientific and methodological works. She also directed interns and graduate students.

Employees and teachers of the university highly appreciated the activity of Valentina Ivanovna Guzeva as vice-rector during difficult years for the country, her attitude to people, honesty and principled in solving questions related to the main directions of the university's work, and in 1999 they elected her rector. It was necessary to put in order the leaking roofs, the dilapidated facades of the university buildings, and to solve other numerous problems of the university.

Since 2000, Valentina Ivanovna has focused on the management of the department, solving scientific problems of child neurology. In addition to training students of various specialties in the disciplines of the department, medical and consultative assistance was provided to patients with severe neurological diseases, diagnostic and therapy methods for children with paroxysmal disorders of consciousness were developed and improved. The department served as a clinical and scientific-methodological base for pediatric neurology for all regions of Russia. Since 2003, the epilepsy school "Epilepsy: achievements and hopes" has been permanently operating at the department.

As part of her teaching activities, Valentina Ivanovna conducts lectures and practical classes with students, residents, postgraduates and attending physicians using modern computer technology, provides counselling to students on organizing educational and scientific work to achieve better results in their studies, as well as long-term consultative and medical assistance to parents of children with serious illnesses.

Since 2012, as the chief freelance children's specialist of the Ministry of health of Russia in the specialty "Neurology", she has been carrying out the assignments and directions of the Ministry of Health. During this period, the procedure for providing medical care for children in the specialty "Neurology" was prepared and approved by the Ministry of Justice and the Ministry of Health, healthcare standards for children in the specialty "Neurology" and Federal Pediatric Neurology clinical guidelines were developed, a specialized commission of chief freelance pediatric neurologists was created and is working, meetings of the chief freelance specialists of the Ministry of Health of the Russian Federation in pediatric neurology are held.

Valentina Ivanovna is a member of the Central Methodical Commission for Neurology of the Ministry of Health of the Russian Federation, member of the certification Commission for neurosciences at the Main Health Department of St. Petersburg, member of the Presidium of the Russian Society of Neurologists, member of specialized dissertation Council of Military Medical Academy named after S. M. Kirov and Chairman of the dissertation specialized Council of St. Petersburg Pediatric Medical University in the specialties "Pediatrics" and "Neurology", member of the European League Against Epilepsy, member of the editorial board of three journals — "Life with Cerebral Palsy. Problems and Solutions", "Pediatrician", Epilepsy and Paroxysmal Conditions", and Deputy Editor of the journal "Pediatric Neurosurgery and Neurology".

Under the guidance of Valentina Ivanovna, 35 candidate and 4 doctoral theses on current problems of neurology were defended. She is the head of a research school in the field of theoretical development and practical implementation of the results of scientific research into paroxysmal conditions in children, conducts scientific work on the development of new methods of prognosis and therapy of patients with severe neurological diseases, in particular, she has developed and implemented into practice scientifically based algorithms for diagnosing epilepsy and non-epileptic disorders of consciousness in children, created a modern program of clinical-instrumental-laboratory diagnosis and correction of cognitive impairments in various neurological diseases in childhood, studied the features of nervous system involvement in full-term and premature newborns, vascular diseases in children and young people, etc.

Since 2007, the Baltic Congress on Child Neurology has been organized and held annually under the leadership of Valentina Ivanovna, since 2014 — with international participation, in which about 1000 pediatricians take part, not only neurologists, but also neonatologists, pediatricians, surgeons, urologists and other medical specialists from various regions of Russia and neighboring countries. Congress participants share their achievements and problems, learn about new scientific findings in the field of child neurology; re-

search schools operate at the congress and training seminars are held.

Valentina Ivanovna gives reports and lectures, takes part in the discussion and development of scientific and practical recommendations on pediatric neurology in various regions of Russia and abroad.

In the last 5 years alone, she has published 143 scientific and methodological works. Among them are 21 scientific articles in journals recommended by the Higher Attestation Commission, 15 educational and methodological recommendations, the Federal Child Neurology Guide, published under her editorship and in which she is the author or co-author of 28 chapters, 21 chapters in 7 monographs, 40 reports at 17 Russian congresses and conferences with international participation on current issues in neurology. Under her leadership, five regular Baltic congresses (IX, X, XI, XII, XIII) were held.

During that period, she conducted studies of the functional activity of the endocrine system depending on gender and the form of epilepsy in children, developed effective methods for correcting therapy for children with paroxysmal disorders of consciousness and a comprehensive etiopathogenetic approach to the diagnosis and treatment of children's epilepsy, substantiated the concept of personalized therapy for epilepsy in children. Valentina Ivanovna also developed new techniques for diagnosing, predicting and treating the consequences of pediatric traumatic brain injury, substantiated methods for treating adult patients with post-traumatic epilepsy depending on nature of injury and duration of hospitalization, identified the diagnostic and prognostic value of the level of antibodies to myelin basic protein in the blood of children with traumatic brain injury, and developed new scientific research areas, according to which 4 candidate theses in the specialty "Neurology" were successfully defended at the Department over this period.

The general list of published scientific and methodological works of Valentina Ivanovna contains about 850 titles, including 25 monographs, an invention patent, 94 articles published in journals recommended by the Higher Attestation Commission.

Currently, she is the head of the Department of Neurology, Neurosurgery and Medical Genetics of the Federal State Budgetary Educational Institution of Higher Education "St. Petersburg State Pediatric Medical University" of the Ministry of Health of the Russian Federation.

In 1999, Valentina Ivanovna was awarded the Certificate of Honor of the Ministry of Health of Russia for many years of productive organizational, scientific and pedagogical activity, in 2014 — the medal "For Merit to National Healthcare", in 2017 — the state award "Honored Scientist of the Russian Federation".

ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 14.05.2024 г.

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «Children's Medicine of the North-West (Детская медицина Северо-Запада)» (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), Пи № ФС77–805334 от 1 марта 2021 г., именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

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Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Children's Medicine of the North-West» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т. е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

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Статья должна иметь **(НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ)**:

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Рекомендуемая структура резюме: введение (Introduction), цели и задачи (Purposes and tasks), материалы и методы (Materials and methods), результаты (Results), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. Объем текста авторского резюме определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах 200–250 слов (1500–2000 знаков).

4. **Ключевые слова** (Keywords) от 3 до 10 ключевых слов или словосочетаний, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «ключевые слова». Предпочтительно использовать ключевые словосочетания из 2–4 слов, наиболее точно отражающих тему статьи. Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются запятой.

5. **Заголовки таблиц, подписи к рисункам**, а также все тексты на рисунках и в таблицах должны быть на русском и английском языках.

6. **Сокращений,** кроме общеупотребительных, **следует избегать.** Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

7. При представлении рукописи в Журнал Авторы несут ответственность за раскрытие своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов. Данная информация должна быть переведена на английский язык.

8. **Литература** (References). Список литературы должен представлять полное библиографическое описание цитируемых работ в соответствии с NLM (National Library of Medicine) Author A.A., Author B.B., Author C.C. Title of article. Title of Journal. 2021;10(2):49–53. Фамилии и инициалы авторов в пристатейном списке приводятся **в порядке упоминания** (1, 2, 3 и т.д.). В описании указываются ВСЕ авторы публикации. Библиографические ссылки в тексте статьи даются цифрой в квадратных скобках. Ссылки на неопубликованные работы не допускаются.

Книга:

Юрьев В.К., Моисеева К.Е., Глущенко В.А. Основы общественного здоровья и здравоохранения. Учебник. СПб.: СпецЛит; 2019.

Никифоров О.Н., ред. Санкт-Петербург в 2021 году. СПб.: Петростат; 2022.

Глава из книги:

Тутельян В.А., Никитюк Д.Б., Шарафетдинов Х.Х. Здоровое питание — основа здорового образа жизни и профилактики хронических неинфекционных заболеваний. В кн.: Здоровье молодежи: новые вызовы и перспективы. Т. 3. М.; 2019: 203–227.

Статья из журнала:

Карсанов А.М., Полунина Н.В., Гогичаев Т.К. Безопасность пациентов в хирургии. Часть 2: Программа менеджмента качества хирургического лечения. Медицинские технологии. Оценка и выбор. 2019;1(35):56–65. DOI: 10.31556/2219–0678.2019.35.1.056–065.

Тезисы докладов, материалы научных конференций:

Марковская И.Н., Завьялова А.Н., Кузнецова Ю.В. Микробный пейзаж пациента первого года жизни с дисфагией, длительно находящегося в ОРИТ. XXX Конгресс детских гастроэнтерологов России и стран СНГ: тез. докл. М.; 2023: 29–31.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». Ч. 1. М.; 2000; 516–519.

Авторефераты:

Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. … канд. психол. наук. СПб.; 2021.

Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: https://rosstat.gov.ru/folder/12781 (дата обращения: 23.10.2023).

Для всех статей необходимо указывать индекс DOI в конце библиографического описания, а также EDN при его наличии.

Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547–52 EDN: YRAEPZ.

Voropaeva E.E., Khaidukova Yu.V., Kazachkova E.A., et al. Perinatal outcomes and morphological examination of placentas in pregnant women with critical lung lesions in new COVID-19 coronavirus infection. Ural Medical Journal. 2023;22(2):109–121. DOI: 10.52420/2071–5943–2023–22–2-109–121 EDN: CXRCMN. (In Russian).

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

Если цитируемая статья написана **на латинице** (на английском, немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования и в и списке литературы, и в References. Пример (статья в норвежском журнале на норвежском языке):

Ellingsen AE, Wilhelmsen I. Sykdomsangst blant medisinog jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести

официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

Стандарт транслитерации. При транслитерации рекомендуется использовать стандарт BSI (British Standard Institute, UK). Для транслитерации текста в соответствии со стандартом BSI можно воспользоваться ссылкой http://ru.translit.ru/?account=bsi.

ФИО авторов, редакторов. Фамилии и инициалы всех авторов на латинице следует приводить в ссылке так, как они даны в оригинальной публикации. Если в оригинальной публикации уже были приведены на латинице ФИО авторов, в ссылке на статью следует указывать именно этот вариант (независимо от использованной системы транслитерации в первоисточнике). Если в официальных источниках (на сайте журнала, в базах данных, в том числе в eLIBRARY) ФИО авторов на латинице не приведены, следует транслитерировать их самостоятельно по стандарту BSI.

Название публикации. Если у цитируемой работы существует официальный перевод на английский язык или англоязычный вариант названия (его следует искать на сайте журнала, в базах данных, в том числе в eLIBRARY), следует указать именно его. Если в официальных источниках название публикации на латинице не приведено, следует выполнить транслитерацию в романский алфавит по стандарту BSI.

Название издания (журнала). Некоторые не англоязычные научные издания (журналы) имеют кроме названия на родном языке официальное «параллельное» название на английском (например, у журнала «Сахарный диабет» есть официальное англоязычное название «Diabetes Mellitus»). Таким образом, для списка References в ссылке на статью из русскоязычного журнала следует указать либо транслитерированное название журнала, либо переводное. Переводное название журнала можно взять либо с официального сайта журнала (или использовать данные о правильном написании англоязычного названия из цитируемой статьи), либо проверить его наличие в базе данных, например в CAS Source Index, библиотеке WorldCat или каталоге Web of Science (ISI), каталоге названий базы данных MedLine (NLM Catalog). В случае, когда у журнала нет официального названия на английском языке, в References нужно приводить транслитерацию по системе BSI. Не следует самостоятельно переводить названия журналов.

Место издания. Место издания в ссылках всегда следует указывать на английском языке и полностью — не в транслитерации и без сокращений. То есть Moscow, а не «Moskva» и не «M.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. В отличие от места издания, название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Примеры перевода русскоязычных источников литературы для англоязычного блока статьи.

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219–0678.2019.35.1.056–065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract. report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma "Mat' i ditya". Part 1: Moscow; 2000; 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание Интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: https://rosstat.gov.ru/folder/12781 (accessed: 10/23/2023). (In Russian).

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's ac-

counts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/47/ (accessed: 11.09.2013).

Пример списка литературы (References):

ЛИТЕРАТУРА

1. Криворученко В.К. Жестокое обращение с ребенком. Проявление и меры предотвращения. Информационный гуманитарный портал Знание. Понимание. Умение. 2012; 3. Доступен по: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (дата обращения: 27.12.2023).

2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231–239. DOI: 10.3238/arztebl.2010.0231.

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1. Krivoruchenko V.K. Child abuse. Manifestation and prevention measures. Informatsionnyy gumanitarnyy portal Znaniye. Ponimaniye. Umeniye. 2012; 3. Available from: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (accessed: 27.12.2023) (In Russian).

2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231–239. DOI: 10.3238/arztebl.2010.0231.

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

Остальные материалы предоставляются либо на русском, либо на английском языке, либо на обоих языках по желанию.

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

Введение, изложение основного материала, заключение, литература. Для оригинальных исследований — введение, методика, результаты исследования, обсуждение результатов, литература (IMRAD).

В разделе «методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

Объем рукописей.

Объем рукописи обзора не должен превышать 25 стр. машинописного текста через два интервала, 12 кеглем (включая таблицы, список литературы, подписи к рисункам и резюме на английском языке), поля не менее 25 мм. Нумеруйте страницы последовательно, начиная с титульной. Объем рукописи статьи экспериментального характера не должен превышать 15 стр. машинописного текста; кратких сообщений (писем в редакцию) — 7 стр.; отчетов о конференциях — 3 стр.; рецензий на книги — 3 стр. Используйте колонтитул — сокращенный заголовок и нумерацию страниц, для помещения вверху или внизу всех страниц статьи.

Иллюстрации и таблицы. Число рисунков рекомендуется не более 5. В подписях под рисунками должны быть сделаны объяснения значений всех кривых, букв, цифр и прочих условных обозначений. Все графы в таблицах должны иметь заголовки. Повторять одни и те же данные в тексте, на рисунках и в таблицах не следует. **Все надписи на рисунках и в таблицахприводятся на русском и английском языках.** Рисунки, схемы, фотографии должны быть представлены в точечных форматах tif, bmp (300–600 dpi), или в векторных форматах pdf, ai, eps, cdr. При оформлении графических материалов учитывайте размеры печатного поля Журнала (ширина иллюстрации в одну колонку — 90 мм, в 2 — 180 мм). Масштаб 1:1.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

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Статьи, поступившие в редакцию, обязательно рецензируются. Если у рецензента возникают вопросы, то статья с комментариями рецензента возвращается Автору. Датой поступления статьи считается дата получения Редакцией окончательного варианта статьи. Редакция оставляет за собой право внесения редакторских изменений в текст, не искажающих смысла статьи (литературная и технологическая правка).

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