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CEREBRAL PALSY: MEDICAL TECHNOLOGIES ARE IMPROVING, BUT THE PROBLEM REMAINS RELEVANT

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ABSTRACT. Despite the achievements of modern medicine, infantile cerebral palsy (ICP) currently remains one of the most pressing problems of both domestic and world health care, dominating in the structure of neurological disorders, leading to severe pathology of the movement system and disability. Often cerebral palsy is combined with other serious disorders of neurological and/or psychiatric nature, causing pronounced persistent limitations of physical abilities and a significant reduction in the quality of life of patients in all aspects. The purpose of this scientific review was to attract the attention of specialists in various areas of health care to the problem of cerebral palsy, as well as to substantiate the earliest necessary medication measures of therapeutic, rehabilitative and preventive profile. Provision of maximum possible, continuous medical care to such children will contribute to the reduction of disability, pronounced functional disorders, and prevent the development of serious complications. The result of early diagnosis and effective treatment can be considered the achievement of individually possible recovery or compensation of impaired functions with the prospect of integration into the surrounding society.

KEYWORDS: *cerebral palsy, etiopathogenesis, diagnosis, treatment, rehabilitation, prevention*

ДЕТСКИЙ ЦЕРЕБРАЛЬНЫЙ ПАРАЛИЧ: МЕДИЦИНСКИЕ ТЕХНОЛОГИИ СОВЕРШЕНСТВУЮТСЯ, АКТУАЛЬНОСТЬ ПРОБЛЕМЫ ОСТАЕТСЯ

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РЕЗЮМЕ. Несмотря на достижения современной медицины, детский церебральный паралич (ДЦП) в настоящее время остается по-прежнему одной из наиболее актуальных проблем как отечественного, так и мирового здравоохранения, доминируя в структуре неврологических нарушений, приводящих к тяжелой патологии системы движения и инвалидизации. Нередко ДЦП сочетается с другими серьезными расстройствами неврологического и/или психиатрического характера, обусловливает выраженные стойкие ограничения физических возможностей и значительное снижение качества жизни пациентов во всех аспектах. Целью настоящего научного обзора послужило привлечение внимания специалистов различных направлений здравоохранения к проблеме ДЦП, а также обоснование наиболее ранних необходимых медикаментозных мероприятий лечебного, реабилитационного и профилактического профиля. Оказание максимально возможной, непрерывной медицинской помощи таким детям будет способствовать снижению инвалидизации, выраженных функциональных нарушений, профилактировать развитие серьезных осложнений. Результатом ранней диагностики и эффективного лечения можно считать достижение индивидуально возможного восстановления или компенсации нарушенных функций с перспективой интеграции в окружающий социум.

КЛЮЧЕВЫЕ СЛОВА: *детский церебральный паралич, этиопатогенез, диагностика, лечение, реабилитация, профилактика*

Nowadays, cerebral palsy in children is a certain group of persistent neurological disorders that develop in the ante-, intra- or postnatal periods and are characterized by organic damage to the brain, in some cases combined with developmental anomalies of the brain. This subsequently leads, to gross defects and serious motor disorders if there is no timely and adequate treatment and rehabilitation.

Despite the fact that this pathology is considered non-progressive, specialists register a strong discrepancy between the constantly increasing demands of the environment on the motor activity of a sick growing child with significantly different parameters of psychomotor and physical development from healthy peers. Ultimately, as a result of irreversible functional and morphological changes in some patients, this ends with the inevitable formation of persistent and pronounced deviations from the norm in neurological profile with the registration of disability in childhood.

In some cases cerebral palsy is combined with severe diseases of the organs of vision and hearing, speech disorders, and is accompanied by decreased intelligence of varying degrees of severity, epilepsy, and other pathologies. These significantly worsens the condition and determines an unfavorable prognosis for health, acquisition of everyday skills, and, in the future, inclusion in educational and work processes, and communication in general.

The search for the most advanced treatment and rehabilitation measures dictates a detailed study of modern views on the etiology and pathogenesis, diagnosis and clinical picture of cerebral palsy [1–5]. The prevalence of cerebral palsy in modern world tends to increase, as evidenced by data from researchers in different countries studying this problem, amounting to 1.5 to 4 and higher per 1000 newborns. There is a direct relationship between the detection of the disease and weight of newborn children: 59.5 per 1000 children with a birth weight of less than 1500 g; 6.2 per 1000 children born with weight of 1500–2499 g; for newborns with weight of 2500 g and above, this value is 1.1 per 1000 children [6].

Perinatal pathology in the Russian Federation is diagnosed in approximately a quarter of the entire child population, while in the structure of neurological pathology leading to disability, cerebral palsy still leads, the prevalence of which is 2–2.5 cases per 1000 children; among all patients with cerebral palsy, about half are premature newborns [7].

According to domestic authors, the following prevalence rates of cerebral palsy are typical for Russia depending on the maturity and birth weight of a child:

- 1.6–6.0 per 1000 full-term newborns;
- 9.0–24.0 per 1000 premature newborns born with a birth weight of 1000–2500 g;
- 18.0–40.0 per 1000 newborns with very low birth weight (less than 1000 g) [8].

Thus, on the one hand, modern high technologies of nursing have increased the survival rate of extremely premature low birth weight babies, and on the other hand, such children have an increased risk of perinatal pathology with the subsequent development of cerebral palsy. So, the shorter the gestational age and the birth weight of the child, the more often cerebral palsy is diagnosed later. In particular, when a child is born before 28 weeks of gestation, the risk of developing cerebral palsy increases by 50 times, while in newborns born at 37–41 weeks, the risk of the disease is 10 times lower [6, 7].

The etiology and pathogenesis of cerebral palsy are currently being comprehensively studied. At the same time, researchers note the primary importance in the genesis of this disease of an unfavorable obstetric and gynecological history and brain damage to a newborn child in the coming months after birth.

When analyzing the age of mothers who gave birth, whose child was subsequently diagnosed with cerebral palsy, the following results were obtained: the majority of women were aged 19 to 30 years — 60.8%; 30 to 39 years — 29.2%; over 40 years — 3.1%; in the younger age group under 18 years of age there were 6.9% of expectant mothers [6].

In literary sources there are some researches on correlation between the birth of a child with cerebral palsy and multiple pregnancy. It was shown that when a pregnant women carrying four fetuses, cerebral palsy occurs in 43% of cases, and if there are triplets and twins — in 8 and 1.5%, respectively, while a singleton pregnancy was associated with a minimal risk of cerebral palsy — 0.2% [6].

The search for key links in the etiology and pathogenesis of cerebral palsy has substantiated the

consideration of causally significant factors depending on their presence in the early periods of a child's development.

Thus, among the causes of antenatal problems (37–60% of cases) as risks of developing motor disorders in the structure of cerebral palsy, maternal diseases of somatic and gynecological genesis, as well as stress and bad habits that complicate the course of pregnancy, are distinguished. Incompatibility of mother and child by blood group or Rh factor may be accompanied by fetal bilirubin encephalopathy with subsequent manifestation of hyperkinetic or dyskinetic syndromes.

Also, factors of damage to the central nervous system (CNS) of the fetus of various origins should be noted. For example, intrauterine infections, intoxications, hypoxic and metabolic disorders, which lead, depending on the timing and degree of exposure, to disturbances in the formation and development of the central nervous system organs, organic brain damage. The problem is especially aggravated by presence of combined genetic pathology [6–12].

In particular, it has been shown that when a pregnant woman becomes ill with a TORCH infection (toxoplasmosis, rubella, cytomegalovirus infection, and herpes infection), the potential risk of cerebral palsy in the child increases.

Such pathologies as neoplasms, uterine scars, morphological and functional disorders of the placenta, including premature placental abruption, chorioamnionitis, are potentially dangerous for the normal neurological development of the fetus.

The presence of antithyroid or antiphospholipid antibodies in a pregnant woman represents severe intoxication for the neurons of the fetus and can cause serious CNS disorders in the future.

Exposure of a pregnant woman to physical trauma can be combined with direct trauma to the fetus and also disrupt the delivery of oxygen and nutrients to the developing organism in utero [7].

Structures of the child's central nervous system, which is formed in utero, are very vulnerable, and throughout the entire pregnancy there is a risk for the formation of various pathologies, characterized by both morphologically diagnosed structural defects and disorders of the conduction system of CNS. Pathologies of structure and disturbances in conduction along the cortex may correspond to both hereditary and sporadic variants of formation.

In addition, fetal stroke of both hemorrhagic and ischemic origin deserves the attention of specialists. It is noted that pregnant women and fetuses have significantly more frequent occurrences of various types of coagulopathies responsible for the risk of hyper- or hypocoagulation during pregnancy [7].

The causes (27–40% of cases) that have a negative impact on the health of the fetus during the intranatal period are considered separately. The risk of developing cerebral palsy increases in cases of premature birth, fetal asphyxia during childbirth caused by the umbilical cord being wrapped around the neck, prolapse of the umbilical cord, amniotic fluid entering the fetus's respiratory tract, bleeding and other complications caused by premature placental abruption or placenta previa. The consequences of birth trauma and cerebral hemorrhages, including those resulting from the use of obstetric forceps and vacuum extractors, are extremely negative, as are the unfavorable consequences of infection directly during childbirth, which can subsequently lead to severe disturbances in the movement system [6–8].

Postnatal risks (3–25% of cases) are primarily represented by head injuries, various infectious diseases and intoxications, as well as oxygen deficiency.

Meningitis and encephalitis, neonatal seizures can result in persistent irreversible brain damage with severe neurological deficit and mental disorders [7, 8].

According to the majority of authors, the clinical manifestation of cerebral palsy usually requires the combined adverse effects of several pathological factors acting in different initial periods of the child's development [6].

Diagnosis of cerebral palsy still presents certain difficulties due to the variability of clinical manifestations and the gradual appearance of characteristic symptoms. However, early diagnosis and timely treatment and rehabilitation measures can significantly improve the health of patients. This is achieved as a result of partial restoration or compensation of impaired motor functions, which, as far as possible in each particular case, optimizes the further prognosis. Researchers emphasize that as a result of adequate, time- and volume-based, comprehensive rehabilitation, pathological

changes can undergo partial or even complete reversal. Specifically, infancy is the most promising period for rehabilitation measures for cerebral palsy, because there is a decrease in in the rehabilitation potential of an elder sick child with a noticeable decrease in the response to treatment, so it is very important not to miss the earliest time for treatment and rehabilitation programs [7].

For the diagnosis of cerebral palsy, it is important to correctly assess clinical symptoms in combination with available modern instrumental methods, using various tests to assess the motor sphere and cognitive functions [13–15].

An important role is played by a comprehensive assessment of health status based on the ICF (International Classification of Functioning) [16, 17].

The basis for the earliest assessment of the health status of children at risk of developing cerebral palsy are the doctor's knowledges of the characteristics of normal neuropsychic development in children of the first year of life.

It is customary to distinguish the following degrees of delay in the level of motor and psychomotor development in cerebral palsy: up to 3 months — mild degree, 3–6 months — moderate degree, over 6 months — severe degree [8].

Considering that about half of children with cerebral palsy are born prematurely, it is fair to introduce correction factors: up to 1 year of life, the period of prematurity in months is added; from 1 year to 2 years of life, it is recommended to add half the period of prematurity in months.

As is known, a clear sequence is typical for the development of the movement system of a healthy child: the extinction of unconditioned reflexes, formation of corrective (straightening) reflexes and improvement of balance reactions.

Researchers emphasize that an early manifestation of cerebral palsy is a violation of the timely reduction (at 2 months in full-term children, at 3–4 months in premature children) of unconditioned reflexes and postural reactions [8].

In addition, in patients with cerebral palsy, tonic reflexes may be present throughout life, which disrupts the development of corrective reflexes, voluntary movements, interferes with normal balance and ultimately results in a pathological postural stereotype in children. Changes in normal muscle tone are typical for such children, which should also alert doctors in terms of the development of cerebral palsy.

The presence of hypertonicity of muscles in children over 4 months in combination with an asymmetrical posture can lead to the development of spastic forms of cerebral palsy, while the frog pose observed with diffuse muscle hypotonia in premature babies may indicate the formation of an atonic-astatic form of cerebral palsy in the future [8].

Thus, the authors identify the following early manifestations of cerebral palsy in children: delayed psychomotor development, absence or delayed reduction of congenital reflexes and tonic reflexes against the background of delayed or absent formation of righting reflexes, which is accompanied by pathology of muscle tone and increased tendon reflexes, the emergence of pathological synkinesis and patological attitudes (flexion and pronation of the arms, adduction of the hip, etc.) [8].

Taking into account the above, it is fair to emphasize that nowadays there is no universal diagnostic algorithm for the early diagnosis of cerebral palsy. At the same time, a number of symptoms can and should attract the attention of doctors immediately after the birth in terms of alertness to the development of this serious disease: a low score on the Apgar scoring system, abnormal muscle tone and movements. Later, as the sick child grows and develops, the pathology of the motor sphere, compared to healthy peers, does not raise doubts among doctors [6].

Among the methods of paraclinical diagnostics, preference is currently given to magnetic resonance imaging of the brain, which is characterized by higher sensitivity compared to computed tomography of the brain and is capable of detecting brain damage at the earliest stages, namely: perinatal hypoxia, cerebrospinal fluid dynamics disorders, and anomalies of intrauterine brain development [6].

Magnetic resonance neuroimaging diagnoses periventricular leukomalacia, ventriculomegaly, areas of cerebral ischemia and hemorrhage [7].

Along with routine electroencephalography (EEG), specialists choose EEG video monitoring of night sleep, which allows for the most detailed assessment of the

Table 1. Medical and psychological diagnostics in cerebral palsy

Таблица 1. Медико-психологическая диагностика при детском церебральном параличе

Медико-психологическая диагностика при детском церебральном параличе / Medical and psychological diagnostics for cerebral palsy				**Иные методы исследования / Other research methods**
Медицинская диагностика / Medical diagnostics			Психологическая диагностика / Psychological diagnostics	Логопедическая диагностика / Speech therapy diagnostics
Осмотр врачами-специалистами / Examination by medical specialists	Лабораторная диагностика / Laboratory diagnostics	Инструментальная диагностика / Instrumental diagnostics	Осмотр медицинским психологом / Examination by a medical psychologist	Осмотр логопедом / Examination by a speech therapist
Педиатр / Pediatrician	Клинический анализ крови / Clinical blood test	Ультразвуковое исследование органов брюшной полости / Ultrasound of abdominal organs	Консультация / Consultation	Консультация / Consultation
Невролог / Neurologist	Биохимический анализ крови / Biochemical blood test	Ультразвуковая денситометрия / Ultrasound densitometry	Тестирование / Testing	Медико-логопедическое исследование при дисфагии / Medical and speech therapy examination for dysphagia
Травматолог-ортопед / Traumatologist-orthopedist	Общий анализ мочи / General urine analysis	Нейросонография / Neurosonography		Медико-логопедическое исследование при дизартрии / Medical and speech therapy examination for dysarthria
Офтальмолог / Ophthalmologist		Магнитно-резонансная томография головного мозга / Magnetic resonance imaging of the brain		
Врач по лечебной физической культуре / Physiotherapy doctor		Компьютерная томография головы / Computer tomography scan of the head		
Физиотерапевт / Physiotherapist		Электроэнцефалография: • с нагрузочными пробами; • с видеомониторингом / Electroencephalography: • with load tests; • with video monitoring		
		Электромиография: • игольчатая; • накожная одной анатомической зоны / Electromyography: • needle-like; • cutaneous of one anatomical zone		

Ending of the Table 1 / Окончание табл. 1

Медико-психологическая диагностика при детском церебральном параличе / Medical and psychological diagnostics for cerebral palsy				Иные методы исследования / Other research methods
		Электроэнцефалография / Electroencephalography		
		Стабиллометрия / Stabilometry		
		Рентгенография: • позвоночника; • головки и шейки бедренной кости / Radiography: • spine; • head and neck of the femur		

functional activity of the brain and identification of focal symptoms.

Depending on the concomitant pathology, children with cerebral palsy are prescribed consultations with specialists: a neurologist, surgeon, orthopedist, ophthalmologist, etc. [6].

Other neurophysiological studies: ultrasound diagnostics, electromyography, recording of evoked potentials in combination with laboratory paraclinical analyses, including biochemical analyses and genetic tests, and consultations with the necessary specialists help to promptly detect concomitant pathology, in particular, optic nerve atrophy, hearing loss and others, as well as diagnose genetic syndromes with manifestation in the first months of a child's life [7].

The scope of medical and psychological diagnostics for cerebral palsy depends on the specific clinical situation (Table 1) [3, 6].

In the structure of concomitant neurological pathology, more than a third of patients are diagnosed with convulsive syndrome, which is more often recorded in the hemiparetic form of cerebral palsy.

Psychiatric disorders are caused by cognitive impairments of various mental functions and occur in over 80% of patients with cerebral palsy. The authors note mental retardation, mental deficiency and speech disorders of varying severity. Only a third of children have normal intelligence. Sensory pathology is observed in approximately 2/3 of clinical cases [8].

According to researchers, concomitant diseases of the sensory organs, cognitive impairment, speech disorders and convulsive syndrome significantly complicate the course of cerebral palsy and seriously affect the quality of life of such children [7].

Thus, the earliest possible diagnosis of cerebral palsy during the first months of life, as well as the identification of concomitant pathology, are important for timely treatment and rehabilitation measures and the most favorable prognosis [8].

Due to the fact that the motor sphere is the central link in the pathology under consideration, the existing classifications of cerebral palsy, as a rule, reflect the characteristic motor disorders in this disease.

In scientific literature, classifications are presented with the allocation of both three and four variants of motor disorders. In the case of three categories, the following forms of cerebral palsy are noted:

- spastic – increased muscle tone and tendon reflexes (upper or lower paraparesis, tetraparesis, unilateral or bilateral hemiplegia);
- dyskinetic – impaired coordination and adequacy of muscle tone regulation (athetoid or hyperkinetic form);
- ataxic – with impaired coordination of voluntary movements (atonic-astatic or mixed forms of cerebral palsy) [7].

According to the classification of four forms, the authors describe: spastic, athetoid, ataxic and mixed variants of cerebral palsy.

However, in practice, specialists more often note spasticity as the dominant symptom, occurring in more than 80% of clinical cases and manifested by

increased muscle tone and tendon reflexes. Less frequently, a decrease in muscle tone with impaired coordination (ataxic form of cerebral palsy) is recorded, as well as instability of muscle tone (dyskinetic form of cerebral palsy). Nevertheless, all forms of cerebral palsy can be accompanied by pathological tonic reflexes, most pronounced when changing body position. In addition, attention is drawn to increased general reflex excitability, pathological synkinetic activity during voluntary movements, as well as pathological variants of coordinating interactions of synergist and antagonist muscles [7, 8].

Currently, according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), it is customary to distinguish the following forms of cerebral palsy:

- G80.0 — Spastic cerebral palsy.
- G80.1 — Spastic diplegia.
- G80.2 — Infantile hemiplegia.
- G80.3 — Dyskinetic cerebral palsy.
- G80.4 — Ataxic cerebral palsy.
- G80.8 — Other cerebral palsy.
- G80.9 — Unspecified cerebral palsy.

Based on the Surveillance of Cerebral Palsy in Europe (SCEREBRAL PALSYE, 2000), the following forms of the disease are diagnosed:

- spastic paralysis — unilateral (hemiplegia), bilateral (diplegia, quadriplegia);
- dyskinetic — dystonic, choreoathetotic;
- ataxic.

In Russia, the classifications proposed by K.A. Semenova (1972) and L.O. Badalyan et al. (1988) are generally recognized among specialists.

The clinical classification of K.A. Semenova provides for the following forms of cerebral palsy: double hemiplegia, spastic diplegia, hemiparetic form, hyperkinetic form, atonic-astatic form, mixed forms.

It has been found that spastic forms of cerebral palsy account for about 90% of all clinical forms, and the percentage ratio of different variants of the disease deserves attention:

- spastic diplegia — 69.3%;
- hemiparetic form — 16.3%;
- atonic-astatic form — 9.2%;
- hyperkinetic form — 3.3%;
- bilateral hemiplegia — 1.9% [6].

According to the domestic classification of L.O. Badalyan et al., cerebral palsy variants are distributed by age periods as follows.

1. Early age corresponds to spastic forms (hemiplegia, diplegia, bilateral hemiplegia), dystonic form, hypotonic form.

2. Older age is characterized by spastic forms (hemiplegia, diplegia, bilateral hemiplegia), hyperkinetic form, ataxic form, atonic-astatic form, mixed forms (spastic-ataxic, spastic-hyperkinetic, ataxic-hyperkinetic) [6].

In addition, the authors defined the stages of development of cerebral palsy: the early stage lasts up to 45 months; the initial residual stage lasts from 6 months to 3 years; the late residual stage is observed in children over 3 years of age.

In scientific literature there is also a classification of cerebral palsy depending on the severity:

- mild — independent movement and mastering of self-care skills is possible;
- moderate — help is needed to move the sick child and to take care of himself;
- severe- the patient is completely dependent on the help of people around him.

Currently, various scales have been developed and are used in practice to objectively assess motor functions in patients with cerebral palsy.

The Gross Motor Function Measure (GMFM) was proposed in 1989 by D. Russell et al. Motor testing is performed from various starting positions: a) lying down and turning; b) sitting; c) crawling on knees; d) standing; e) while walking, running and jumping. Depending on the version, the scale is presented with 88 or 66 tests that can be independently completed by a healthy child aged 5 years. Testing time is from 45 to 60 minutes.

The Gross Motor Function Classification System (GMFCS) is a functional classification of cerebral palsy proposed in 1997 by R. Palisano et al. In this case, the level of motor development and limitations of motor activity in everyday life are taken into account, the functional capabilities of patients, and the need for special devices to perform movements are assessed. The classification includes 5 levels for 4 groups of children of different ages: up to 2 years; 2 to 4 years; 4 to 6 years; 6 to 12 years [6, 8].

The GMFCS-E&R classification was developed in 2007, adding an adolescent group from 12 to 18 years

old, taking into account the anatomical and physiological characteristics of this age period. It has been shown that after 12 years, a decrease in children's motor activity is recorded, which is due to intensive growth, active formation of contractures and significant inhibition of the development of new motor functions.

According to this classification, the following levels are provided:

- Level 1 — the child is able to move without restrictions and assistance;
- Level 2 — movement with restrictions, the child does not go outside the premises;
- Level 3 — the child moves using devices and assistive devices (walkers, sticks, crutches, orthoses);
- Level 4 — motorized means are needed for movement, since independent movement is sharply limited;
- Level 5 — the child's movements are completely dependent on others, transportation is carried out in a stroller or wheelchair [6, 8].

International criteria for assessing the functional state of children with cerebral palsy also include the Barthel index, modified for children under 4 years of age, the functional independence scale, modified Wee Fim for children over 4 years of age, the Manual Ability Classification System, and the Ashworth spasticity assessment scale.

Thus, the main clinical symptoms of cerebral palsy are disorders leading to pathology of motor function and coordination: paresis, spasticity, fine motor disorders, dystonic attacks, hyperkinesis. With prolonged illness and pronounced morphofunctional changes, serious complications develop, which include dislocations and subluxations of joints (in 2/3 of patients), foot deformities in over 80% of patients, contractures, pathological postural settings, deformities of joints and limbs, for the correction of which the surgical intervention may be used [7].

Drug treatment of cerebral palsy is exclusively symptomatic and is aimed at correcting a specific symptom or complication of the disease. The tasks of drug therapy include correcting muscle tone, preventing cicatrix and commissures, and improving the psychoemotional background [7].

Among pharmaceutical preparations, the following groups can be noted: nootropic and neurotrophic agents; preparations that restore cerebral hemodynamics and microcirculation; normalize metabolic processes in the nervous system, and also have reparative and resolving properties; anticonvulsants; preparations that correct muscle tone; agents for the treatment of hyperkinesis; general tonic preparations, including vitamin and microelement complexes [8].

In order to correct local and segmental spasticity of the lower and upper extremities, intramuscular administration of botulinum toxin type A preparation is indicated, which can reduce spasticity for up to 3–5 months. In Russia, botulinum therapy has been included in the treatment standards for cerebral palsy since 2004. Two preparations of botulinum toxin type A are registered for use in children over 2 years of age: Dysport for focal spasticity of the lower extremities and Botox for focal spasticity associated with dynamic foot deformity of the equine foot type [18–24].

Orthopedic treatment includes orthopedic shoes and insoles, verticalizers, reclinators, functional splints, tutors, and layings. This treatment helps to prevent contractures and is aimed at restoring the correct position of the limb.

Orthotics are an important part of the multidisciplinary rehabilitation program for patients with cerebral palsy and are performed in the form of semi-soft splinting. The main goals of using orthoses are to increase function, prevent deformations, maintain the joint in a functional position, stabilize the trunk and limb, selectively facilitate movement control, reduce spasticity, and protect the limb in the postoperative period.

Fixed contractures that develop as a result of long-standing muscle spasticity may be considered from the point of view of the appropriateness of surgical intervention. The most frequently used operations for cerebral palsy are tenotomise. The purpose is to return the limb to its normal supporting position as much as possible. In cases of severe symmetrical spasticity that does not respond to medication, accompanied by pain syndrome or joint complications, neurosurgeons recommend spinal rhizotomy to interrupt the transmission of pathological impulses from the spinal cord to the affected muscle groups. Also among the indications for surgical treatment are severe manifestations of scoliosis, pathology of the joints and feet [25, 26].

Taking into account very serious prognosis for the health and life of children with cerebral palsy due to the presence of limited health capabilities and disabilities, inevitably facing psychological trauma and lack of tolerance in society, especially with intact intelligence, patients need comprehensive assistance and support at all levels of treatment and rehabilitation, educational and upbringing processes, inclusion in educational and industrial organizations, and obtaining a profession. For this reason, in addition to health care workers, the active participation of a clinical psychologist, speech therapist, defectologist, occupational therapist and social workers is required [27, 28].

Comprehensive rehabilitation of patients with cerebral palsy includes medical, psychological, social, educational, training (with the formation of everyday skills), educational and work components [29, 30].

The program of rehabilitation treatment for children with cerebral palsy depends on the nature, severity and predominant localization of the lesion, as well as the presence of concomitant pathology [30, 31].

Under the guidance of a physical and rehabilitation medicine physician, a multidisciplinary team actively selects the most effective interventions and routing plan for a specific patient [32–40].

The complex of treatment and rehabilitation measures, along with drug-based therapeutic and surgical interventions, according to indications, includes methods of physical rehabilitation (therapeutic exercise, massage, mechanotherapy, physiotherapy, manual therapy, reflexology), psychological, pedagogical and speech therapy correction, including high-tech speech therapy using computer-controlled communication tools for patients with severe speech problems; psychotherapy, occupational therapy with elements of career guidance [41–43].

Great importance is given to the social and environmental adaptation of patients and psychological assistance to the family. Hippotherapy, canine therapy and dolphin therapy can be recommended, which have a positive effect on the psycho-emotional background and motor sphere.

Thus, the tasks of specialists still include a high degree of alertness in terms of early diagnosis and timely adequate treatment of cerebral palsy.

Today, only early effective and prolonged necessary medical interventions can provide significant assistance to patients with cerebral palsy, reduce the percentage of disability and severe functional disorders.

Comprehensive treatment, rehabilitation and preventive measures should further become an integral and important part of the lives of patients suffering from cerebral palsy.

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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CORONAVIRUS INFECTION AND COVID-19 IN CHILDREN. PART 1. EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS

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ABSTRACT. The lecture presents data on the epidemiology of coronaviruses as causative agents of seasonal respiratory viral infections in children, as well as the SARS-CoV-2 virus, which caused the COVID-19 pandemic. The classification, morphology and structure of seasonal coronaviruses are given. The source and transmission routes of the pathogen in a new coronavirus infection are shown, attention is paid to the role of COVID-19 as an infection associated with healthcare. The structural features of SARS-CoV-2, its antigenic determinants that ensure penetration of the virus into target cells, as well as the main and alternative mechanisms of virus penetration into cells are described. Target cells that highly express entry receptors for SARS-CoV-2 are indicated. The pathogenesis of the new coronavirus infection, as well as pathomorphological changes in organs and tissues in COVID-19 in children, are presented in detail

KEYWORDS: *COVID-19, children, etiology, epidemiology, pathogenesis*

КОРОНАВИРУСНАЯ ИНФЕКЦИЯ И COVID-19 У ДЕТЕЙ. ЧАСТЬ 1. ЭПИДЕМИОЛОГИЯ, ЭТИОЛОГИЯ, ПАТОГЕНЕЗ

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РЕЗЮМЕ. В лекции представлены данные об эпидемиологии коронавирусов как возбудителей сезонных респираторных вирусных инфекций у детей, а также о вирусе SARS-CoV-2, который вызвал пандемию COVID-19. Приведена классификация, морфология и структура сезонных коронавирусов. Показаны источник, пути передачи возбудителя при новой коронавирусной инфекции, уделено внимание роли COVID-19 как инфекции, связанной с оказанием медицинской помощи. Описаны особенности строения SARS-CoV-2, его антигенные детерминанты, обеспечивающие проникновение вируса в клетки-мишени, а также основные и альтернативные механизмы проникновения вируса в клетки. Указаны клетки-мишени, которые высоко экспрессируют рецепторы входа для SARS-CoV-2. Подробно представлен патогенез новой коронавирусной инфекции, а также патоморфологические изменения в органах и тканях при COVID-19 у детей.

КЛЮЧЕВЫЕ СЛОВА: *COVID-19, дети, этиология, эпидемиология, патогенез*

EPIDEMIOLOGY

Coronaviruses (causative agents of seasonal viral infections in children) are a group of viruses that causes zoonotic infections transmitted between animals (mammals, birds, amphibians and, presumably, reptiles) and humans; they belong to the genus *Alphacoronavirus* and *Betacoronavirus*, order *Nidovirales*, family *Coronaviridae*, subfamily *Coronaviridae* [1]. The viruses can cause epidemic and even pandemic processes, and the disease proceeds with multisystemic damage of varying severity [2]. Currently, more than 40 types of coronaviruses are known, the list of which is constantly expanding due to spontaneous mutations, so all types of coronaviruses can potentially be dangerous to humans. There are four subfamilies of coronaviruses: *Alphacoronavirus*, *Betacoronavirus*, Gammacoronavirus and *Deltacoronavirus*. The ***Alphacoronavirus*** subfamily includes 2 subgenera, each of which includes one species of coronaviruses of medical significance (the subgenus *Davinalovirus* includes the species *HCoV 229E* and the subgenus *Setracovirus* includes the species *HCoV NL63*). The ***Betacoronavirus*** subfamily includes 5 species of coronaviruses of medical significance, which are divided into 3 subgenera: *Embecovirus* (two species— *HCoV HKU1*, *HCoV OC43*), subgenus *Merbecoronavirus* (species *MERS-CoV*) and subgenus *Sarbecovirus* (species *SARS-CoV* and *SARS-CoV-2*), ***Gammacoronavirus*** *and* ***Deltacoronavirus*** [1, 3]. Nowadays, *Alphacoronavirus* and *Betacoronavirus* pose a danger to people.

The coronavirus was first isolated by A.F. Schalk, M.C. Hawn (1931) and described as an infectious bronchitis virus in chickens [4]. The first publications on respiratory diseases caused by coronaviruses in human date back to 1965, when a description of acute respiratory infection (ARI) appeared in a British child with the isolation of the pathogen *α-coronavirus* group 1, initially described as isolate B814, then defined as HCoV-229E human coronavirus, causing *human coronavirus disease 229E*, and in 1967 K. Mcintosh discovered coronavirus in a tracheal cell culture [5–8]. In 1968, coronaviruses were grouped into the *Coronavirus* group [7], which appeared in the catalogues of the International Committee on Taxonomy of Viruses (ICTV) in 1971. In 1976, the taxonomic rank was raised from genus to family [2]. In 1996, at the 10th International Virology Congress, a taxonomic group was proposed — an order called *Nidovirales* (from Latin *nidos* — nest). In 1967–1972, a number of cases of ARI in adults were recorded, the causative agent of which was β-coronavirus (*HCoV-OC43 from group 2 of lineage A, human coronavirus OC43*). In 2004, coronaviruses HCoV-HKU1 of lineage A of group 2 *β-coronaviruses* and HCoV-NL-63 were isolated, and in 2005, HcoV HKU1 was found [2].

Until 2004, the existence of four representatives of the *Coronavirinae* family, subfamily *Orthocoronavirinae (HCoV 229E, HCoV NL63, HCoV HKU1, HCoV OC43)* was known, which, circulating year-round, caused from 15 to 30% of annual cases of ARI, which, as a rule, occurred with damage to the upper respiratory tract of mild or moderate severity; no fatal outcomes were established [9–11]. However, in 2003–2004, an outbreak of atypical pneumonia of coronavirus etiology was noted in China, which was named severe acute respiratory syndrome (SARS), and the *β-coronavirus SARS-CoV* of group 2 lineage B (reservoir — bats) was isolated. Eight years later, in 2012, in the city of Jeddah, Saudi Arabia, during a study of nasopharyngeal swabs taken from a man with ARI, the *β-coronavirus SARS-CoV* of group 2 lineage C — *MERS-CoV* (middle east respiratory syndrome coronavirus) was isolated. Its reservoir is dromedary camels. The virus caused the Middle East respiratory syndrome (MERS). Both viruses had the ability to spread in epidemics, and outbreaks of coronavirus infection were registered in the world, while the mortality rate of patients, including those under 18 years of age, during the first outbreak was about 10%. The cause of death of 774 people in 37 countries was confirmed. During the second episode, the mortality rate reached 40%. By 2020, 866 deaths from MERS were registered, which forever secured the status of *life-threatening for the coronavirus infection*. Since 2004, no new cases of atypical pneumonia caused by SARS-CoV have been registered, but MERS-CoV continues to circulate and cause new cases of the disease [2, 8, 12].

PANDEMIC OF THE NEW CORONAVIRUS INFECTION

The new coronavirus that entered human circulation at the end of 2019 is a highly homologous copy of SARS-CoV (79%) and MERS-CoV (50%). On February

11, 2020, the International Committee on Taxonomy of Viruses assigned the official name SARS-CoV-2 (*Betacoronavirus*, assigned to pathogenicity group II) to this virus [13–15]. The virus had a lower severity of the diseases it caused and lower mortality rates, and determined the ***pandemic of a new coronavirus infection*** that began on December 8, 2019, in Hubei Province (Wuhan City) of the People's Republic of China. It was there that the first case of a human disease caused by an unknown pathogen was officially registered, and on January 7, 2020, a new virus belonging to the *Coronaviridae* family was identified, temporarily named *2019-nCoV* (from English novel coronavirus 2019). On January 10, 2020, Genbank published the complete genome of the 2019-nCoV virus strain (*Wuhan-Hu-1* under number MN908947, RefCeq NC_045512) for the first time. On January 30, 2020, with a large number of infections and deaths, the World Health Organization (WHO) declared the ongoing outbreak caused by the 2019-nCoV virus a public health emergency of international concern. WHO has renamed the 2019-nCoV virus to *SARS-CoV-2* (severe acute respiratory syndrome 2 — SARS coronavirus 2). On February 1, 2020, WHO assigned the official name of the infection caused by *SARS-CoV-2* to be COVID-19 (Coronavirus disease — 2019). On March 11, 2020, a pandemic was declared [16, 17].

The main variants of SARS-CoV-2 have evolved during the pandemic from pre-alpha, alpha and delta to omicron, the highly transmissible variants of which have led to an increase in the incidence and hospitalization of children in many countries around the world, including Russia [18, 19]. Children became the main source of the spread of the virus, since its release into the environment occurs not only during the incubation period, but also within 7–14 days after the complete resolution of the clinical picture of the disease. As variants of the dominant virus strains changed, the severity of disease in children changed significantly, and by 2021, most patients had mild symptoms (58%) or no symptoms (36%), and hospitalization rates dropped from 10% to 0.2%. By early May 2023, the COVID-19 epidemic situation was assessed by WHO as favorable, which made it possible to lift the international emergency regime and declare the end of the pandemic on May 5, 2023.

MORPHOLOGY AND STRUCTURE OF CORONAVIRUSES AND SARS-COV-2 VIRUS

Analysis of the SARS-CoV-2 genome has shown thatit is very similar to the genome of bat coronaviruses, and the receptor-binding domain of the spike

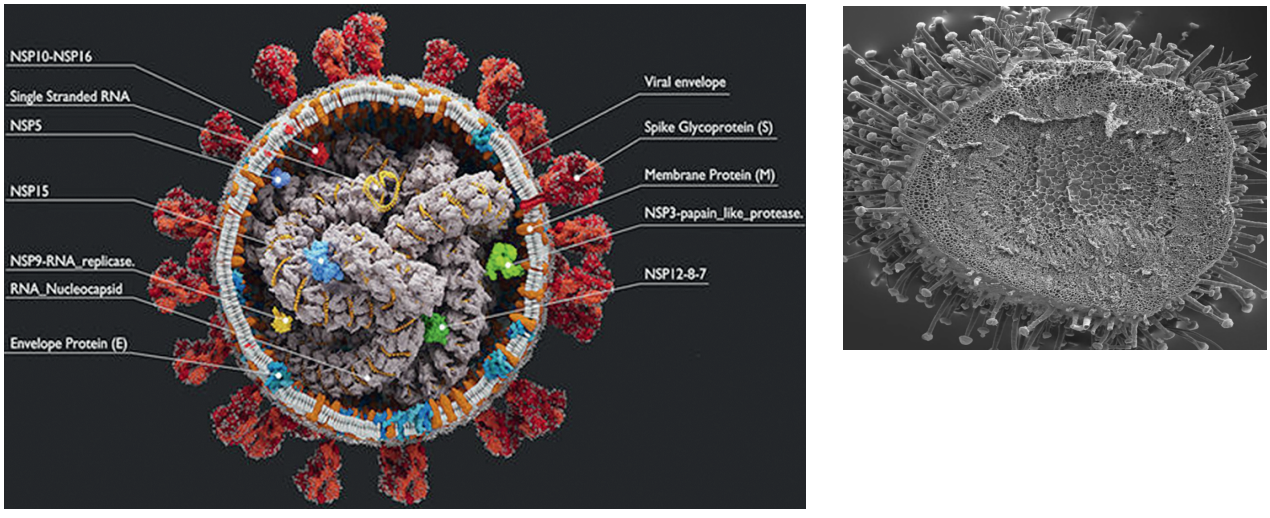


Fig. 1. The structure of coronaviruses (Source: https://img-new.cgtrader.com/items/2534580/8fe84e53e0/large/corona-virus-scientifically-accurate-3d-model-3d-model-obj-fbx-blend-abc-gltf-usdz.jpg)

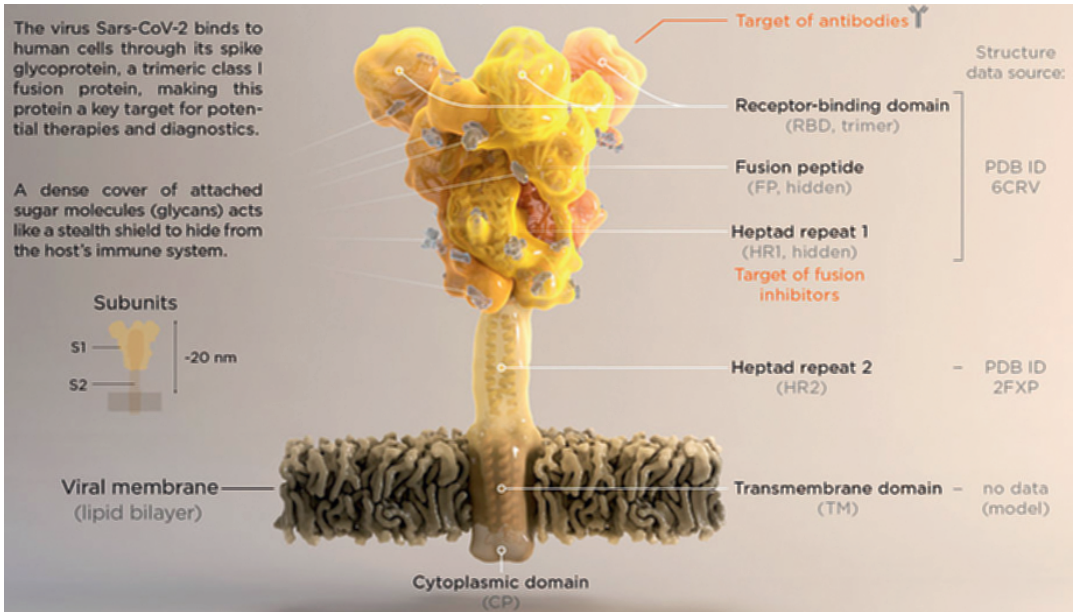
Рис. 1. Строение коронавирусов (Источник: https://img-new.cgtrader.com/items/2534580/8fe84e53e0/large/corona-virus-scientifically-accurate-3d-model-3d-model-obj-fbx-blend-abc-gltf-usdz.jpg)

glycoprotein is similar to the Malayan pangolin coronavirus. Therefore, SARS-CoV-2 likely originated from a bat-derived CoV and was transmitted to humans via an unknown mammalian intermediate host, possibly the Malayan pangolin. In addition, the SARS-CoV-2 S1/S2 spike protein cleavage site has acquired a furin site that is absent in bats and pangolins, which may indicate natural selection either in the host animal before zoonotic transfer or in humans after zoonotic transfer [20].

All coronaviruses have the same morphological properties and structure, although some species have differences (Fig. 1) [2].

HCoV virions are spherical in shape with diameters ranging from 80 to 229 nm and are the largest among RNA viruses.

The RNA of coronaviruses has helical symmetry and is located inside the ***nucleoprotein***, which forms the ***nucleocapsid*** covered by the ***supercapsid membrane*** consisting of a lipid bilayer. **Structural proteins** are located underneath. The ***spike protein*** (150–220 kDa) is located on the surface of the lipid bilayer of the virus in the form of club-like processes, which gives the virus a crown shape. It is a glycoprotein that creates trimers in the form of peplomers, which form the "teeth of the crown" and ensure the penetration of the virus into the



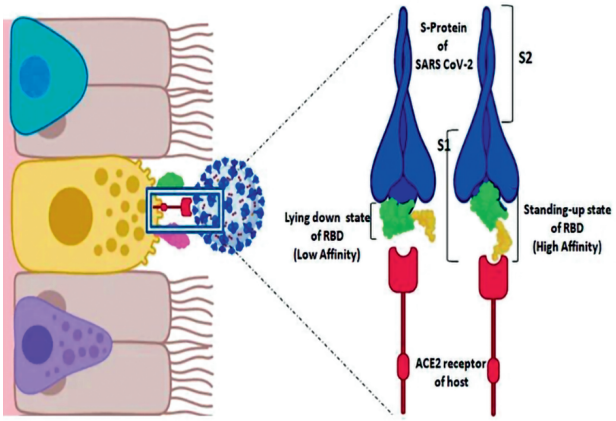


Fig. 2. Structure of the spike protein (SP) of the SARS-CoV-2 virus (Source: https://svrobo.org/where-are-the-robots-when-you-need-them/)

Рис. 2. Строение спайк-протеина (SP) вируса SARS-CoV-2 (Источник: https://svrobo.org/where-are-the-robots-when-you-need-them/)

cell. ***M-protein*** (23–25 kDa) is a transmembrane glycoprotein that provides the shape of the virion and controls particle size and assembly efficiency and is located deeper than the SP. The ***N-protein*** (50–60 kDa) is a phosphorylated protein by chemical structure and protects the viral RNA, keeping it in a stable state within the viral envelope. The ***E-protein*** (9–12 kDa) is enveloped, adjacent to the nucleocapsid, and is found only among viruses of the *Orthocoronavirinae* subfamily. Its pentamers form ion channels and are an important pathogenicity factor. The protein can bind to gene-regulating proteins, alter the pattern of human gene activation, and participate in virion assembly and virion release outside the cell. In some coronaviruses (*HCoV-OC43* and *HCoV-HKU1*), an additional surface protein is detected. It is called ***hemagglutinin esterase*** (HE protein, 9–12 kDa), which is a glycoprotein [2, 4, 8, 9, 20]. Viruses that have the HE protein have hemagglutinating and esterase activities, which they use as a mechanism for penetrating target cells. ***There no HE protein in all particularly dangerous viruses (SARS-CoV, MERS-CoV, SARS-CoV-2)*** [2].

SARS-CoV-2 has four conserved structural proteins (SP, E, M, and N) [21] and accessory proteins (3a, 6, 7a, 7b, 8b, 9b) that may influence the infectivity and pathogenicity (e.g., 3a and 7a activate ion channels, increase NF-κB activity, and enhance the induction of host target cell apoptosis) of the virus [22]. SARS-CoV-2 SP is a trimeric glycoprotein (6–8 million Da) with three domains: an *ectodomain* (subdomains S1, the receptor-binding subunit, and S2, the membrane-bound subunit), a *transmembrane region*, and an *intracellular domain* that has a short intracellular tail [23]. S1 SP contains the N (N-terminal domain — NTD) and C (C-domain — CTD) domains [22] (Fig. 2).

In this case, S1-CTD acts as a receptor-binding domain (RBD) that interacts with ACE-2 (zinc-dependent peptidase of the renin-angiotensin system) entry receptor for SP. The RBD SP determines viral tropism and infectivity, and is responsible for viral attachment to the target cell membrane and cell entry. Therefore, any RBD mutation may have a significant impact on SARS-CoV-2 receptor binding [22]. The S2 domain is the membrane fusion subunit and contains the fusion peptide (FP), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), and transmembrane domain (TM). S2 has two cleavage sites, one at the S1/S2 border (R685) and the other at S2 (R815). HRs trimerize to form a helical structure and pull the viral envelope and host cell membrane bilayer into close proximity, facilitating their fusion [22]. At the junction of the S1 and S2 subunits of SP there is a "*furin site*" that is cleaved by furin, a host cell protease contained in lysosomes, which greatly simplifies the interaction of SP with TMPRSS2 (transmembrane serine protease 2) and increases the rate of viral entry into the cell.

The CTD domain is the receptor-binding domain for SARS-CoV-2, which recognizes **ACE2** [24, 25] — *a zinc-dependent peptidase of the renin-angiotensin system* — a type I transmembrane glycoprotein [12], as an entry receptor. It functions as a monocarboxypeptidase, catalyzing the cleavage of angiotensin II (Ang II), which is responsible for systemic vasoconstriction and aldosterone release and also has prooxidant and proinflammatory effects. During the process, the heptapeptide angiotensin 1–7 (Ang 1–7) is formed, which counteracts the action of the Ang II peptide, causing vasodilating, antiproliferative and antifibrotic effects) [12].

For effective penetration of the virus into the cell, activation of the TMPRSS2 SP [26], its cleavage and attachment to the active zones of ACE2 are required. TMPRSS2 has three functional domains and mediates the first cleavage of the SP at the S1–S2 boundary (R685) and the second at the S2' regions (R815) [27]. The virus's entry into the cell is aided by its receptor-binding domain (RBD), which SARS-CoV-2 releases when capturing the cell and which more effectively "latches" to ACE2, allowing the virus to enter the cell 4 times faster than SARS-CoV [28].

Note. The "Omicron" variant and its varieties ("Centaur", "Ninja", etc.) are characterized by reduced binding of SP to TMPRSS2 and the presence of multiple mutations in SP (17 in RBD; 8 in NCD). Moreover, both domains are immunodominant targets for neutralizing antibodies produced by COVID-19 vaccines and antibodies in those who have recovered; 10 mutations in the SP region that contacts the ACE2 receptor, combined with its 2.4-fold decrease in the ability to bind to soluble sACE2 and be cleaved by furin; high stability of SP, difficulty in cleaving S1; mutations in S2, etc. This makes the strain the most transmissible among all SARS-CoV-2 variants, which leads to a decrease in its virulence, facilitates easy and rapid invasion into target cells, and also increases the resistance of the virus to vaccines with neutralizing antibodies [29–31].

PATHOGENESIS OF COVID-19

The source of infection is a sick person and/or human in the incubation period, as well as an asymptomatic carrier. The greatest danger to others is posed by a sick person in the last two days of the incubation period and the first days of the disease. **The pathogen is transmitted** mainly by ***airborne droplets*** (when coughing, sneezing, talking) at a close distance (less than 2 meters) [32]; ***airborne dust***, less often by ***contact*** (when shaking hands and other types of direct contact with an infected person), as well as through food products, surfaces and objects contaminated with the virus [1, 33].

The vast majority of infections occur through contact with clinically manifested cases in family clusters (75–85%); transmission of infection from asymptomatic children to adults is possible [34]. Also possible: **fecal-oral** route, because SARS-CoV-2 RNA was detected in fecal samples from 8 out of 10 pediatric patients examined for several weeks after recovery and normalization of nasopharyngeal swabs [35]. **Sexual** transmission is possible: the virus was detected in the semen of 15.8% of those infected, 26.7% of them had an acute infection, and 8.7% were considered recovered [36]. The **transplacental** route is also possible, and the basis of vertical transmission of the virus from mother to fetus is placental vasculopathy (maternal viremia, placental infection lead to inflammation of the placenta and neonatal viremia) [37–39]. The possibility of vertical transmission is 5.3%, the incidence of COVID-19-positive newborns is 8% [40]. RNA of the virus or antibodies to SARS-CoV-2 are detected in vaginal fluid (4.6%), umbilical cord blood (6%), umbilical cord (6%), placental tissue (12%), amniotic fluid (5.6%), and breast milk (5%) [41]. The presence of PCR-positive throat swabs in newborns born to mothers with COVID-19 immediately after birth, as well as SARS-CoV-2 virus-specific IgM and IgG antibodies in blood serum, confirms the possibility of vertical transmission of infection [42, 43]. However, IgM antibodies are not able to penetrate the placenta, which may indicate intrauterine infection of the child. The incidence of infected newborns was almost 2 times higher in cesarean sections (5.3%) than in vaginal deliveries (2.7%) [44].

Note. **The role of COVID-19 as a healthcare-associated infection has been established.** Healthcare workers are at the highest risk of infection because they have prolonged aerosol contact while performing their professional duties. The risk of airborne, dust and contact-household transmission of the pathogen increases in conditions of non-compliance with the requirements of the sanitary and anti-epidemic regime, epidemiological safety rules, including the use of personal protective equipment. There is also a risk of the formation of epidemic foci of COVID-19 in organized groups and groups of closed-type organizations if infection prevention measures are not followed.

It is known that at room temperature, SARS-CoV-2 can remain viable in various environmental objects for several hours to 3 days, while in dried form — up to 3 days, in a liquid medium — up to 7 days. The virus remains stable over a wide range of pH values (up to 6 days at pH 5 to 9 and up to 2 days at pH 4 and pH 11). At a temperature of +4 °C, the virus remains stable for more than 14 days. When heated to 37 °C, the virus is completely inactivated within 1 day, at 56 °C — within 45 minutes, at 70 °C — within 5 minutes. The virus is sensitive to ultraviolet radiation and the action of various disinfectants in working concentrations [16].

The virus penetrates target cells that have ACE2 receptors, which are highly expressed in the epithelial cells of the mucous membrane of the nose, mouth, tongue, and salivary glands, which explains the loss of smell and impaired taste perception during the development of clinical symptoms of COVID-19 [12]. It also penetrates the conjunctiva of the eyes [16], as well as the epithelium of the bronchi and lungs, but in alveolocytes, the expression of ACE2 is significantly higher than in the bronchi, while type II alveolocytes, which produce surfactant, express ACE2 in 83% of cases in relation to type I alveolocytes [45]. The virus is tropic to the epithelial cells of the stomach, duodenum, ileum and rectum, which explains the occurrence of abdominal and dyspeptic syndromes in patients [46, 47] and in the proximal tubules of the kidneys, bladder [12, 47–49]. Also the virus penetrates cardiomyocytes, the membrane of pericytes, which regulate the permeability of the blood-brain barrier and the lumen of blood vessels [12, 46]. The virus penetrates the syncytiotrophoblast (STB), villous cytotrophoblast (VTB),

extravillous trophoblast (EVTB), endothelium, vascular smooth muscle cells and decidual cells of the placenta [50], in umbilical cord cells [51], in the epithelium and stroma of the endometrium in the secretory phase compared to the proliferation phase [52], in vagina, and also in the tissues of the mammary glands, which does not exclude the possibility of infection of breast milk [53, 54].

Note. Endothelial cells, fibroblasts, perivascular macrophages do **not express ACE2**, but synthesize the VWF factor (von Willebrand factor, a plasma glycoprotein that attaches platelets to the damaged area of the vessel). Pericytes, which normally do not come into contact with whole blood, when infected with the SARS-CoV-2 virus, create the opportunity to influence the functions of the vascular endothelium, which significantly changes the thrombogenetic function of the blood [55]. ACE2 is not expressed in the liver, hepatocytes, Kupffer cells, but is found in cholangiocytes [46].

Most frequently, SARS-CoV-2 interacts with goblet cells of the nasal epithelium, type II alveolocytes and enterocytes. At the same time, glutamyl aminopeptidase may be the second probable receptor for the virus [10]. ACE2, TMPRSS2 and FURIN are co-expressed in human lung tissue, so SARS-CoV-2 replication is significantly higher in the lungs. When the virus is inoculated into the respiratory tract, *mucociliary clearance activity* is suppressed by inhibiting the motility of epithelial cilia, which leads to the death of epithelial cells. The *surfactant system*, its production and function are *destroyed*, which leads to the collapse of the alveoli, and as a result of a sharp disruption of gas exchange, acute respiratory distress syndrome (ARDS) develops. *The permeability of cell membranes increases and there is an increased transport of albumin-rich fluid into the interstitial tissue of the lung and the lumen of the alveoli* [3]. In intestinal epithelial cells, two serine proteases (TMPRSS2 and TMPRSS4) are expressed at once, and their co-expression also contributes to the most pronounced aggression from SARS-CoV-2 [56, 87]. This may explain the very frequent manifestation of COVID-19, especially in children, with intestinal manifestations.

The consequence of the binding of the SARS-CoV-2 NTD SP to mACE2 is the proteolytic activation of the spike proteins by host cell proteases and the penetration of the SARS-CoV-2/ACE2 complex into the cell via the mechanisms of fusion of the virion membrane with the host cell membrane or by endocytosis [57]. Following the initial interaction between the S1 domain and ACE2, the S2 segment mediates the fusion of the host cell membrane and the viral membrane. This allows the SARS-CoV-2 RNA genome to enter the host cells. This is followed by viral RNA replication, assembly of new virions, and their exit from the cell. New viral particles are released into the extracellular space via exocytosis. The ACE2 receptor is internalized by the infected cell, resulting in its downregulation [57].

Note. **Alternative mechanisms of virus penetration into target cells are described:** the use of cathepsin L (CTSL), which ensures the penetration of the virus into the cell through the formation of endosomes; with the participation of furin, elastase, factor X or trypsin, which prepare SP by cleaving it into smaller fragments [58]; via the protease ADAM17, it cleaves ACE2; using the co-receptors neuropilin-1 (NRP1), heparin sulfate (HS), which promote binding between SP and ACE2 [59]; by binding to C-type immune cell lectins (DC-SIGN, Langerin, MGL, MR, Dectin-1 and Mincle), which are expressed by dendritic cells and macrophages, which leads to suppression of their function, causing the release of proinflammatory cytokines and induction of T-lymphocyte apoptosis, which may result in an immune response in the form of a cytokine storm [60]. One of mechanisms is interacting with polysaccharides of pulmonary microbiome bacteria [61, 62], which can cause respiratory tract infections; by binding to the target cell membrane antigen, the CD147 protein (basigin), which promotes the penetration of the virus into cells by endocytosis, its expression increases susceptibility to SARS-CoV-2 infection [63, 64]. Although CD147 does not bind to ACE2, CD147 silencing reduces ACE2 levels through an as yet unknown mechanism [61, 65, 66]) and performs a large number of physiological functions in the body, including the activation of extracellular matrix metalloproteinases, which ensure the restructuring of the intercellular substance in tissues [66]. Glucose-related protein 78 (GRP78) promotes viral entry by acting as a receptor or stabilizing the binding between SP and ACE2 [67, 68]. Both CD147 and GRP78 are tumor markers [69], which explains why cancer patients have a higher risk of severe COVID-19. Another mechanism is carried out through the interaction of the coronavirus protein Orf9b with the human mitochondrial chaperone protein (TOM70), which affects the synthesis of type I IFN and increases the replication of the SARS-CoV-2 virus [70]. This variant of protein interaction is common

to all three epidemically significant coronaviruses (SARS-CoV-1, MERS-CoV and SARS-CoV-2), which allows us to consider this type of binding (Orf9b-TOM70) pathogenetically important and causing not only the insufficiency, but also the perversion of the innate immune response and interferonogenesis in the first day of COVID-19. The consequence of this is uncontrolled replication, accumulation of viral particles and increased viral load with the subsequent development of a hyperinflammatory immune response by the 7th-10th day of COVID-19 disease. All factors that regulate the expression of the ACE2 gene contribute to more efficient penetration of the virus into cells. SARS-CoV-2 can also invade target cells through mechanisms of hemoglobin (β-1 chain) blocking, porphyrin binding and inhibition of heme synthesis, which affects the nature of the immune response [71]. All alternative mechanisms of SARS-CoV-2 virus invasion not only significantly increase its interaction with target cells, but can also determine the possibility of vertical transmission of infection from mother to fetus.

SARS-CoV-2 can downregulate ACE2 expression by directly binding to the receptor on endothelial cells, resulting in overactivation of the ACE2/Ang II/AT1 axis and inhibition of the ACE2/Ang-(1-7)/MasR axis. This results in the development of vascular pathological changes such as increased permeability, inflammatory response and oxidative stress. This leads to disruption of endothelial function and degradation of endothelial junction proteins, including disruption of the blood-brain barrier, which contributes to fluid extravasation and the development of vasogenic edema [72]. The possibility of specific damage to lymphocytes by the virus with their apoptosis and pyroptosis has also been proven, which underlies prognostically unfavorable lymphopenia, macrophage activation syndrome and hemophagocytic syndrome, and deficiency of neutrophils as one of the causes of ARD syndrome.

Dissemination of SARS-CoV-2 from the systemic bloodstream or through the ethmoid plate leads to brain damage. Changes in the sense of smell (anosmia) in patients at an early stage of the disease may indicate both CNS damage by the virus, which penetrates primarily through the olfactory nerve, and damage to the cells of the nasal mucosa.

The critical form of COVID-19 is a type of cytokine storm, and its manifestations are similar to the course of primary and secondary hemophagocytic syndrome (macrophage activation syndrome). Moreover, the cytokine storm is a predictor of mortality in patients with COVID-19 [74].

Note. In the critical course of COVID-19, pathological activation of innate and adaptive (Th1 and Th17 types) immunity, dysregulation of the synthesis of proinflammatory, immunoregulatory, anti-inflammatory cytokines and chemokines (IL-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (GKSF), granulocyte-macrophage colony-stimulating factor (GMKSF), tumor necrotizing factor alpha (TNF-α), IFN-α and IFN-β and others, as well as inflammation markers (CRP, ferritin) develop. Patients with severe COVID-19-infection develop vascular endothelial dysfunction, coagulopathy, thrombosis with the presence of antibodies to phospholipids, with a clinical picture resembling catastrophic antiphospholipid syndrome. Cytokine storm in COVID-19, as a rule, leads to the development of acute respiratory distress syndrome (ARDS), multiple organ failure and can be fatal [16, 75–77].

The severity of the inflammatory response in COVID-19 depends, on the one hand, on the virulence of the pathogen, and on the other, on the immune resistance of the host organism. In low-virulence strains of SARS-CoV-2, the primary site of virus fixation is the ciliated epithelial cells of the upper respiratory tract, which leads to the development of mild, sometimes asymptomatic infections [78]. The highly virulent SARS-CoV-2 strain infects type II alveolar cells and triggers the secretion of a large number of proinflammatory cytokines and chemokines (IL-2, IL-7, IL-10, G-CSF, TNF-α, etc.), to a lesser extent activates the secretion of TNF-α and IL-6, and very minimally - IFNα / β [79, 80]. As a result, severe pulmonary dysfunction occurs due to inflammation and edema caused by viral proliferation in the lung tissue, which ultimately disrupts alveolar gas exchange. Such changes lead to hypoxia, including cerebrovascular type [81].

An intermediate product of SARS-CoV-2 replication is the formation of ssRNA, which triggers the activation of the antiviral program in the cell. This results in the induction of expression of more than 300 IFN I-related genes (ISG), which together determine the antiviral status of the cell through the synthesis of a huge number of antiviral proteins, cyto- and chemokines, as well as interferon-related enzymes, which leads to inhibition of the spread of the virus. Moreover, SP SARS-CoV-2 is a key inhibitor of IFN I synthesis activation, blocking

the induction of IFN synthesis, which prevents the initiation of the innate antiviral immune response and makes the patient with COVID-19 defenseless against infection [21].

PATHOMORPHOLOGY OF COVID-19

Pathological examination of lung tissue did not reveal any specific macroscopic signs of COVID-19, although the morphological picture can be considered characteristic [16]. *Lung damage in COVID-19 is characterized by pronounced plethora of capillaries of the interalveolar septa, as well as branches of the pulmonary arteries and veins, with a slowdown in blood flow, erythrocyte sludge, fresh fibrin and organizing thrombi; intrabronchial, intrabronchiolar and intraalveolar hemorrhages, which are a substrate for hemoptysis, as well as perivascular hemorrhages.*

Patients with critical COVID-19 develop vascular endothelial dysfunction, coagulopathy, thrombosis with the presence of antibodies to phospholipids, with a clinical picture resembling catastrophic antiphospholipid syndrome. Clinical and pathological changes are difficult to differentiate from multiorgan thrombosis developing with ARDS and thrombotic microangiopathy (TMA).

The SARS-CoV-2 virus is detected in ciliated cells of the bronchi, bronchiole epithelium, alveolocytes and macrophages, as well as in the vascular endothelium.

Specific viral and cytokine storm-induced, and at a later stage, possibly autoimmune, damage to the endothelium, called *SARS-CoV-2-associated endothelial dysfunction* and even endotheliitis, and hypercoagulation syndrome are the basis of the thrombotic microangiopathy characteristic of COVID-19, mainly in the lungs, less often in other organs (myocardium, brain, kidneys, etc.), and thrombosis of large arteries and veins (often with thromboembolism). The possibility of platelet activation by antibodies to SARS-CoV-2 as an important cause of the development of hypercoagulation syndrome is not excluded.

Changes have also been identified in other organs that can presumably be associated with the generalization of coronavirus infection or immune disorders. Changes may occur in the *intestines* (catarrhal and hemorrhagic gastroenterocolitis, ischemic lesions), *brain and pia mater* (encephalitis, meningitis, hypoxic and ischemic lesions), heart (myocarditis, acute coronary syndrome), *pancreas, kidneys, spleen, testicles*.

Skin manifestations typical of COVID-19 are described (from hemorrhagic syndrome to various types of rashes). The pathogenesis is unclear. There is evidence that SARS-CoV-2 is capable of activating previous chronic infectious processes.

The second part of the lecture will describe the clinical picture, diagnosis and treatment of coronavirus infection.

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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PRACTICAL ASPECTS OF ORGANIZATION OF ENTERAL NUTRITION IN PEDIATRIC INTENSIVE CARE UNIT PATIENTS. PART 1. CHOOSING A NUTRITIONAL STRATEGY

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ABSTRACT. The provision of enteral nutrition is an important component of a multimodal system of therapy. Failure to meet the energy needs of patients in critical conditions against the background of hypercatabolism leads to a more severe course of diseases, increased hospitalization time and lethality. Lack of independent nutrition in pediatric intensive care units (PICU) leads to the need for artificial nutrition, mainly enteral nutrition through special devices (probes, feeding stomas). Anatomo-physiological features of children of different ages necessitate a differentiated approach to the choice of devices and algorithms of general and special care. The article substantiates the necessity of using an individualized approach in the organization of enteral nutrition of children hospitalized in intensive care units with the help of special devices.

KEYWORDS: *enteral nutrition, nutritional support in PICU, tube-feeding*

ПРАКТИЧЕСКИЕ АСПЕКТЫ ОРГАНИЗАЦИИ ЭНТЕРАЛЬНОГО ПИТАНИЯ ПАЦИЕНТОВ ПЕДИАТРИЧЕСКИХ ОРИТ. ЧАСТЬ 1. ВЫБОР СПОСОБА ПИТАНИЯ

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РЕЗЮМЕ. Обеспечение энтерального питания является важным компонентом мультимодальной системы терапии. Неудовлетворение энергетических потребностей пациентов в критических состояниях на фоне гиперкатаболизма приводит к более тяжелому течению заболеваний, увеличению длительности лечения в стационаре и летальности. Отсутствие возможности самостоятельного питания в отделениях реанимации и интенсивной терапии (ОРИТ) у детей приводит к необходимости проведения искусственного питания, преимущественно энтерального, через специальные устройства (зонды, питательные стомы). Анатомо-физиологические особенности детей разного возраста трактуют необходимость дифференцированного подхода к выбору таких устройств и алгоритмов общего и специального ухода. В статье обоснована необходимость использования индивидуализированного подхода при организации энтерального питания детей, госпитализированных в отделения реанимации и интенсивной терапии, с помощью специальных устройств.

КЛЮЧЕВЫЕ СЛОВА: *энтеральное питание, нутритивная поддержка в ОРИТ, tube-feeding*

INTRODUCTION

Providing enteral nutrition to patients hospitalized in intensive care units (ICU) is an integral part of any multimodal therapeutic strategy for disease treatment [1–3]. Children, unlike adults, are more sensitive to starvation due to insufficient reserves of energy substrates in the body and increased metabolic needs [4]. Nutritional support has an undoubted positive effect on the condition of the gastrointestinal mucosa, affecting the microbiota. In the absence of maldigestion, nutritional support ensures the supply of substances necessary not only for recovery, but also for maintaining the physical and mental development of a child [5–7]. It is especially important to ensure energy needs in patients hospitalized in ICU, given that most of them have varying degrees of protein-energy malnutrition or are at high risk of its development [8, 9]. Organization of enteral nutrition for patients with dysphagia is of great importance [10–12]. Enteral nutrition using a special device (tube-feeding) not only ensures the satisfaction of nutritional needs, but in some cases can lead to a reduction in the risk of aspiration syndrome [13, 14].

AIM

To propose effective practical recommendations for organizing enteral nutrition for children hospitalized in intensive care units.

CHOOSING A METHOD OF ENTERAL NUTRITION

Providing nutritional support to ICU patients is associated with a number of difficulties. The most common problems are associated with the inability to eat independently or the presence of contraindications to it.

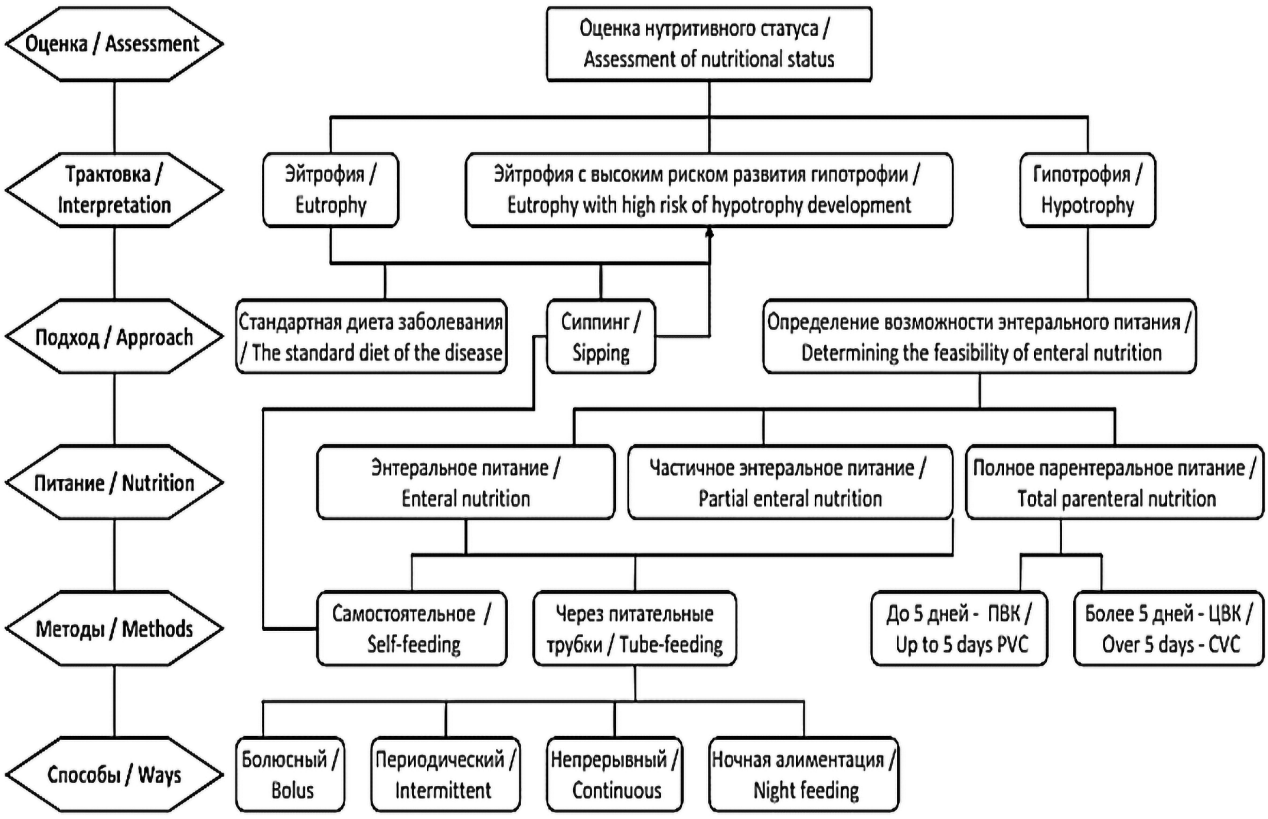

Fig. 1. Algorithm for selecting a nutritional support method. PVC — peripheral venous catheter; CVC — central venous catheter

Рис. 1. Алгоритм выбора метода нутритивной поддержки. ПВК — периферический венозный катетер; ЦВК — центральный венозный катетер

In diseases accompanied by acute cerebral, respiratory, cardiovascular failure, and artificial ventilation, independent nutrition is impossible [15]. Another group includes not only patients in the early postoperative period after facial interventions, but also patients with severe forms of cardiovascular or respiratory failure, in which physical activity during meals leads to increased hypoxia [15]. In diseases that were previously considered absolute contraindications to the start of enteral nutrition, such as necrotizing enterocolitis, toxic megacolon, Ogilvie's syndrome, peritonitis, gastrointestinal bleeding and high intestinal fistulas, it is now possible to use trophic nutrition in a volume of 0.1–20 ml/kg per day [16–19].

The choice of the method of nutritional support depends on the clinical and nutritional status of a child, the expected duration of artificial feeding and the need to use special devices for delivering a formula (Fig. 1) [16, 20]. In addition, there are various problems associated with the degree of swallowing disorder. For non-invasive detection of dysphagia and its severity in children depending on age, the functional oral intake scale (FOIS) is used (Table 1) [21–23]. Daily assessment using the FOIS allows not only timely detection of dysphagia and its severity, but also the determination of therapeutic strategies, in particular, the use of compensatory techniques associated with modification of the food texture, as well as the use of special devices. In this case, texture is determined not only by the consistency of food, but also by the rheological (viscosity) and structural (density, surface tension for liquids) properties of food, as well as the type of cooking.

Table 1. The functional oral intake scale

Таблица 1. Функциональная шкала приема пищи через рот

Дети менее 1 года / Infants	**Уровень / Level**	**Дети 1–18 лет / Children aged 1–18 years**
Ничего через рот / Nil per os	1	Ничего через рот / Nil per os
Искусственное питание через зонд с минимальными попытками приема пищи или жидкости / Tube dependent with minimal attempts of food or liquids	2	Искусственное питание через зонд с минимальными попытками приема пищи или жидкости / Tube dependent with minimal attempts of food or liquids
Искусственное питание через зонд с параллельным постоянным пероральным прием пищи или жидкости / Tube dependent with consistent oral intake of food or liquids	3	Искусственное питание через зонд с параллельным постоянным пероральным прием пищи или жидкости / Tube dependent with consistent oral intake of food or liquids
Расширение перорального приема с постепенным изменением текстуры пищи (от жидкой до густой и твердой в зависимости от возраста) / Expanding oral intake with gradual changes in food texture (from liquid to thick and solid depending on age)	4	Пероральная диета одной пюреобразной консистенции / Total oral diet of a single consistency
	5	Полный пероральный рацион различной консистенции, но требующий специальной подготовки или компенсации / Total oral diet with multiple consistencies, but requiring special preparations or compensations
	6	Полный пероральный рацион различной консистенции без специальной подготовки, но с определенными ограничениями в еде / Total oral diet with multiple consistencies without special preparation, but with specific food limitations
Полный пероральный прием с постепенным расширением диеты от жидкой до густой и твердой в зависимости от возраста / Full oral intake with gradual expansion of the diet from liquid to thick and solid depending on age	7	Полный пероральный рацион без ограничений / Total oral diet with no restrictions

Inextricably linked to consistency, food texture is a broader concept defined by mechanical, tactile, and in some cases visual and auditory receptors. Enteral nutrition is carried out by introducing a nutritional formula into the stomach (gastric method) or small intestine (jejunal or postpyloric method), depending on the clinical situation and technical capabilities of the medical organization.

ADMINISTRATION OF NUTRITION FORMULA INTO THE STOMACH

When providing nutritional support for up to 30 days and implementing a night alimentation program, an oro-/nasogastric tube is used [24–26]. If long-term artificial nutrition is required, independent food intake is impossible, gastroesophageal reflux disease (GERD) is present and progresses, and aspiration syndrome occurs, gastrostomy is recommended [16, 20, 25, 27, 28], including percutaneous endoscopic (PEG) and laparoscopic gastrostomy [24, 28–34].

The introduction of less invasive gastrostomy techniques has improved the efficiency of nutrition in seriously ill children [35]. In particular, laparoscopic methods are a safe alternative in cases of severe scoliosis, obesity, strictures and other congenital or acquired diseases of the esophagus with stenosis of its lumen, and other contraindications to endoscopic gastrostomy. In cases of severe GERD, recurrent aspiration pneumonia, and uncontrollable vomiting, gastrostomy is recommended to be performed simultaneously with fundoplication [36–38]. An indication for early gastrostomy is initially severe dysphagia in patients with cerebral palsy IV–V according to the EDACS (Eating and Drinking Ability Classification System). A feeding duration of more than 4 hours per day or more than 30 minutes per feeding, as well as any duration of feeding with progression of nutritional deficiency are indications for gastrostomy [39].

The advantages of gastric access include maintaining the cyclic release of intestinal hormones, which has a positive effect on the regeneration of the intestinal mucosa [16, 40]. In addition, being more physiological, the method reduces the risk of developing osmotic diarrhea. The method is cheap and available in all medical organizations [40].

In case of absolute contraindications to the installation of an oro- or nasogastric tube, nutrition is provided through a tube inserted into the jejunum (nasojejunal tube, jejunostomy). Postpyloric methods of introducing enteral formula are recommended in cases of high risk of aspiration, uncontrolled GERD, ineffectiveness of nutritional correction, and refusal of parents or legal representatives from fundoplication. To prevent regurgitation of food into the stomach, the distal end of the tube should be located more than 40 cm distal to the ligament of Treitz [41]. Complications of this method of nutritional support include the development of osmotic diarrhea and maladaptation of gastric motility.

Enteral tube feeding can be performed as a bolus, intermittently or continuously [15, 42]. Bolus feeding has a number of important advantages: imitation of physiological reactions of the endocrine system, free feeding regime, ensuring the required temperature of the nutritional mixture. However, it is not recommended for postpyloric feeding methods due to the high risk of developing dumping syndrome and diarrhea [43]. Intermittent administration allows the rate to be adjusted depending on food tolerance. Continuous feeding can be used throughout the day, separately during the day or night (night alimentation), and is recommended in cases of intolerance to the formula, and jejunal feeding [26, 44]. A combination of continuous night feeding with boluses is possible when there is a need to meet high energy needs or intolerance to food volume [24]. In this case, bolus feeding can be carried out using mixtures whose consistency, according to the International Dysphagia Diet Standardisation Initiative (IDDSI) scale, corresponds to 0–1, since mixtures with a higher viscosity require more pressure for insertion into a probe or gastrostomy tube, often causing obstruction of their lumen [45, 46]. Thicker formulas (IDDSI 1–3) can be administered using special enteral feeding pumps — enteromats [46]. The rate of introduction of the mixture depends on the age and weight of the child, while at the beginning of enteral support, the initial rate is set, and when the volume of food is absorbed, and there are no complications or adverse effects, the rate of introduction is increased to the maximum (Table 2) [16]. However, the assignment of the food volume must correspond to the anatomical

Table 2. Age-specific features of the rate of nutrition introduction

Таблица 2. Возрастные особенности скорости введения питания

Тип введения / Type of introduction	**Болюсное введение / Bolus feeding**			**Непрерывное введение / Continuous feeding**		
Возраст, лет / Age, years	**0–1**	**1–6**	**>7**	**0–1**	**1–6**	**>7**
Начальный объем / Initial feeding volume	10–15 мл/кг каждые 2–3 часа / 10–15 ml/kg every 2–3 hours	5–10 мл/кг каждые 2–3 часа / 5–10 ml/kg every 2–3 hours	90–120 мл/кг каждые 3–4 часа / 90–120 ml/kg every 3–4 hours	1–2 мл/кг каждый час / 1–2 ml/kg every hour	1 мл/кг каждый час / 1 ml/kg every hour	25 мл/кг каждый час / 25 ml/kg every hour
Увеличение объема / Increased nutritional intake	10–30 мл на каждое кормление/ 10–30 ml per feeding	30–45 мл на каждое кормление / 30–45 ml per feeding	60–90 мл на каждое кормление / 60–90 ml per feeding	1–2 мл/кг каждые 2–8 часов / 1–2 ml/kg every 2–8 hours	1 мл/кг каждые 2–8 часов / 1 ml/kg every 2–8 hours	25 мл/кг каждые 2–8 часов / 25 ml every 2–8 hours
Допустимый объем одного кормления / Suggested tolerance volumes	20–30 мл/кг каждые 3–4 часа / 20–30 ml/kg every 4–5 hours	15–20 мл/кг каждые 4–5 часов / 15–20 ml/kg every 4–5 hours	330–480 мл каждые 4–5 часов / 330–480 ml every 4–5 hours	6 мл/кг каждый час / 6 ml/kg every hour	1–5 мл/кг каждый час / 1–5 ml/kg every hour	100–150 мл каждый час / 100–150 ml every hour

and physiological characteristics of the sizes of the gastrointestinal tract organs. The need to ensure energy needs that exceed the ability to be absorbed by volume is the basis for using hypercaloric formulas.

In the prospective multicenter observational study by E.E. Martinez et al. (2022), when analyzing the effectiveness of continuous and bolus feeding in 1375 critically ill children on mechanical ventilation, no differences were found between the methods in providing energy and protein needs, as well as the development of infectious complications [47]. Similar results were obtained in a systematic review by P. Rohani et al. (2022) [14].

Conducting artificial nutrition through special devices leads to the "switching off" of the oral cavity from the digestion process and a number of negative consequences. On the one hand, the influence of nutrition on the excitation of receptors of the oral mucosa and sensory fibers of the V, IX and X pairs of cranial nerves has been proven [20]. On the other hand, there is a lack of wetting of the food bolus with saliva, which contains more than 50 enzymes that promote not only the initial digestion of food, but also the protection of the mucous membrane of the oral cavity and esophagus [20]. In addition, prolonged absence of oral nutrition leads to the development of dysphagia due to oral inactivity as one of the components of the "learned non-use" phenomenon, in which there is a disconnection of the sensorimotor processes of food consumption from the intake of the nutritional formula [11]. Therefore, oral feeding should always be encouraged, provided that safety conditions for the child are met and there is no severe dysphagia [48].

The decision to administer enteral nutrition using special tubes installed in the stomach or intestine is made not only in accordance with the anatomical and physiological characteristics, but also taking into account the presence of GERD, gastroparesis of any etiology, and the risk of developing aspiration syndrome [43]. In 2023, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) prepared guidelines for healthcare professionals on infant feeding, which demonstrated the positive effect of mixed foods, including blended or pureed forms [45].

TUBE FEEDING

Enteral tube feeding is the most commonly used method. The access of choice is often through the nasal passages, however, in some cases, it is possible to place it through the mouth. Insertion of a gastric tube is a standardized invasive procedure that is most often performed blindly by nurses, attending physician. When inserting the tube, it is necessary to achieve the correct position of the distal end, which normally reaches the stomach (3–10 cm below the lower esophageal sphincter). If the insertion depth is insufficient, the end and side holes of the probe end up in the esophagus, which increases the risk of aspiration. If the tube is inserted too deeply, it may become kinked in the stomach, become knotted, bend upwards into the esophagus, or, after passing through the pyloric section, the distal section, be installed into the duodenum, which increases the risk of developing dumping syndrome.

Several techniques are used to determine the length to which the tube will be installed. The most common is the "nose-earlobe-xiphoid process" technique, proposed in 1951 [49–51]. This technique allows accurate length determination in approximately 72.4% of cases [52]. A prospective study by Taylor et al. (2014) found increased risks of transpyloric or transesophageal positioning when using the nose-earlobe-xiphoid process + 10 cm technique in adults and older children [53].

A.J. Csaldo et al. (1992) suggested calculating the depth of insertion of an orogastric tube based on a length equal to 9.7 cm + 0.226 × patient height (cm), and a nasogastric tube equal to 8 cm + 0.252 × height (cm) [54, 55]. Taking into account the identified difficulties, A.J. Csaldo et al. (2002) suggested calculating the depth of probe insertion by the length calculated as the sum of the measurements of the distances from the nose or corner of the mouth to the earlobe and from the earlobe to the point midway between the xiphoid process and the navel [56].

Taking into account the anatomical and physiological characteristics of children, I.M. Vorontsov and A.V. Mazurin pointed out the need to determine the length of the probe placement based on the length of the esophagus (Table 3) [57]. In addition, to calculate the distance from teeth to the stomach entrance, the formula 20±n is used, where n is the child's age in years. The length of the esophagus can be calculated using the formula: height (cm) × 0.2 + 6.3 cm [58].

In full-term newborns, the formula for calculating the length of nasogastric tube insertion is based on a child's length: 1.95 cm + 0.372 × length (cm) [59]. In addition, in 2011, M.L. Cirgin Ellett et al. proposed a table of predictive length of nasogastric tube insertion for newborns (Table 4) [59].

K.J. Gallaher et al. in 1993 proposed minimum values for the depth to which the tube is inserted, corresponding to 13 cm for infants weighing <750 g, 15 cm for infants weighing 750–999 g, 16 cm for infants weighing 1000–1249 g, and 17 cm for infants weighing 1250–1499 g [60]. For children over 1 month and up to 18 years old, formulas proposed by M.L. Ellett et al. in 2012 can be used (Table 5) [55].

To determine the tube diameter, a scale proposed by Joseph Frederic Benoit Charrière is used, where 1 F,

Table 3. Esophageal length as a function of age [57]

Таблица 3. Длина пищевода в зависимости от возраста [57]

Возраст, годы / Age, years	Длина, см / Length, cm	Расстояние от зубов до входа в желудок, см / Distance from teeth to stomach entrance, cm
Новорожденный / Newborn	8–10	16–20
1	12	20–22
2	13	22,5–24
5	16	26–27,9
10	18	27–33
15	19	34–36
Взрослые / Adults Мужчины / Men Женщины / Women	 25 (23–30) 23 (20–26)	40

Table 4. Length of nasogastric tube insertion from birth to 1 month of age [59]

Таблица 4. Длина введения назогастрального зонда от рождения до 1 месяца [59]

Длина новорожденного, см / Newborn length, cm	Длина введения трубки, см / Tube insertion length, cm	Длина новорожденного, см / Newborn length, cm	Длина введения трубки, см / Tube insertion length, cm
35,0–35,5	15,0	47,0–47,5	19,5
36,0–37,0	15,5	48,0–49,0	20,0
37,5–38,0	16,0	49,5–50,5	20,5
38,5–39,5	16,5	51,0–51,5	21,0
40,0–41,0	17,0	52,0–53,0	21,5
41,5–42,0	17,5	53,5–54,5	22,0
42,5–43,5	18,0	55,0–55,5	22,5
44,0–45,0	18,5	56,0–56,5	23,0
45,5–46,5	19,0		

Table 5. Formula for calculating the length of probe placement depending on age [55]

Таблица 5. Формула расчета длины постановки зонда в зависимости от возраста [55]

Возраст, месяцев / Age, months	Вид зонда / Type of tube	Формула расчета по длине тела, см (L) / Formula for calculating body length, cm (L)
1–28	Назогастральный / Nasogastric	= 14,8 + 0,19 × L
	Орогастральный / Orogastric	= 13,3 + 0,19 × L
29–100	Назогастральный / Nasogastric	= 18,3 + 0,19 × L
	Орогастральный / Orogastric	= 16,8 + 0,19 × L
>100	Назогастральный / Nasogastric	= 16,6 + 0,22 × L
	Орогастральный / Orogastric	= 15,1 + 0,22 × L

Fr or Ch (Charrière) is equal to 0.33 mm. For visual differentiation, tube connectors are color-coded according to diameter size. To select the correct tube, it is necessary to take into account its diameter at the point with the narrowest (projection of the upper edge of the 3rd thoracic vertebra) and widest (projection of the upper edge of the 7th thoracic vertebra) lumen [61]. It is especially important to determine anatomical changes in the region of the upper point in the presence of esophageal dysphagia [62].

When placing a nasogastric tube, the structural features and dimensions of the lower nasal passage should be taken into account. It has been shown that the diameter of the inferior nasal passage in 78.7% of children of the first year of life is less than 2.0 mm, in toddlers – 2.0 mm, in children 4 to 6 years old – 2.7 mm, in children over 7 years old – 2.7–3.3 mm [63]. Similar data were obtained using craniometry with a detailed study of the width of the inferior nasal passage. It was determined that the width of the inferior nasal passage at the level of an anterior edge of the inferior turbinate at the age of 1–1.5 years is 2.5±0.1 mm, at the level of the posterior edge – 2.3±0.1 mm, by 2–3 years – 3.2±0.1 mm and 3.1±0.1 mm, respectively, with a subsequent increase in the inferior nasal passage by 0.2–0.3 mm in each age group of children, reaching 3.9±0.1 mm at the level of the anterior edge of the inferior turbinate and 4.0±0.4 mm at the level of the posterior edge of the inferior turbinate at 13–16 years [64]. Additionally, soft tissue structures narrow the lumen.

Thus, the diameter of the probe should be minimal to prevent trophic complications, sinusitis, and nosebleeds. However, given the high probability of probe occlusion during blender feeding, it should be no less than 18–24 Fr [76].

The main methods for monitoring the correct installation of the probe are:

1) "gold standard" – X-ray /computed tomography of the abdominal organs [43, 55, 65-68];
2) ultrasound examination of the stomach [69, 70];
3) pH-metry of gastric aspirate using test strips or standard laboratory tests (normal pH should be ≤5) [71–74];
4) colorimetric capnometry or capnography [68, 75];
5) aspiration test;
6) test with the introduction of air and simultaneous auscultation of sounds in the projection area of the stomach.

When using the tube for a long time, the material from which it is made is of significant importance [77]. Polyvinyl chloride tubes are the cheapest, and due to their appropriate rigidity they can be inserted without a conductor. Low adhesion of the nutrient mixture and medicinal substances prevents rapid obturation of the tube lumen. However, low biocompatibility with tissues, corrosion by gastric and intestinal contents, leading to hardening during prolonged use, as well as the presence of phthalates and plasticizers in the composition determine the period of use of the tube no more than 3–7 days. Silicone tubes are the softest and most flexible, which determines the best tolerance by patients when using them, and rarely cause allergic reactions and trophic disorders. However, the absence of a semi-rigid frame leads to both difficulties during placement, which determines the need to use conductors, and to complications in the form of kinks during use. Polyurethane tubes have sufficient rigidity when installed. The walls soften after implantation when the patient's body temperature is reached. This makes it possible to install polyurethane probes without conductors. Such probes are somewhat inferior to silicone ones in terms of ensuring patient comfort during use. The technology for producing probes has made it possible to reduce the wall thickness, which relatively increases the internal lumen compared to tubes made of other materials. In addition, in some cases it is possible to install tubes in the postpyloric sections, which is achieved not only by the appropriate length of the tube, but also by the presence of olives. Polyurethane tubes also have good biocompatibility, do not change their physical characteristics when interacting with gastric and intestinal contents. Silicone and polyurethane tubes can be used for up to 4–6 weeks if care requirements are met.

NUTRITION THROUGH STOMA

Children with initial protein-energy malnutrition, aggravated by the premorbid background, are often admitted to ICU already with a gastrostomy tube. In some cases, gastrostomy is performed in ICU, especially during long-term hospitalization, the presence of oropharyngeal or esophageal dysphagia of various etiologies, as part of the preparatory stage for surgical interventions. Care of a gastrostomy tube in children requires special attention, since it is a technological device that requires specific procedures: careful attachment of the tube to the body; fixation of the outer part and prevention of dislocation of the elements of the gastrostomy tube. The placement of gastrostomy tubes with a diameter greater than 18–20 Fr should be avoided due to the increased incidence of complications [68, 76].

After gastrostomy, it is necessary to control and eliminate pain. Traditionally, feeding is preferred to be postponed for up to 24 hours after gastrostomy due to concerns about suture failure and food leakage from the stomach into the abdominal cavity. However, the possibility of starting feeding 3 hours after the operation, depending on the severity of the condition, has been confirmed [78–80].

Daily inspection of the postoperative wound makes it possible to promptly identify signs of inflammation and other complications. To prevent infectious complications, dressings are applied using aseptic bandages. After the wound has completely healed, it is necessary to rotate the gastrostomy tube by 180–360° and move it up and down by approximately 1–2 cm at the stoma site to prevent granulation. To prevent obstruction, it is necessary to select the consistency of the formula (according to IDDSI no more than 0–3) with the diameter of the tube.

Studies on enteral nutrition in adults have shown that percutaneous endoscopic gastrostomy in the areas of the posterior wall or along the greater curvature of the stomach are significant risk factors for both early and late complications [81]. This may be due to the relatively large distance between the walls of the stomach and the abdominal wall, which increases the tension of the gastrostomy tube during gastric contraction, causing slow or incomplete fistula formation, increasing the risk of perforation, bleeding, peritonitis. The anatomical and physiological features of the stomach in children suggest a similarly high risk of developing such complications.

PRINCIPLES OF ORGANIZING CHILDREN'S NUTRITION IN THE ICU

A child's serious condition is not a reason to stop feeding if the child has effective breathing and swallowing and can be fed orally. In some cases, sipping therapy is prescribed in addition to independent feeding (see Fig. 1). If the patient's condition is stable and organizational and technical capabilities are available, it is recommended to involve trained parents in feeding the child. When eating, regardless of the method, the following rules must be observed.

1. Prepare the child's favorite dishes.
2. Maintain a 5–6 meal regimen, more often if necessary.
3. When feeding independently, initially prepare a small portion.
4. Do not serve the dish too hot or cold.
5. The temperature of the administered formula should be 37–37.5 °C [15, 76, 84].
6. Isolate the child from food odors if they cause nausea.
7. Ventilate the ward or box after eating.
8. Carefully monitor hygiene when feeding the child (hand washing rituals before and after eating, oral hygiene, hand hygiene of those feeding).
9. During feeding, place the child in a sitting or semi-sitting position with the head end raised to prevent choking and aspiration.
10. When feeding in bed, it is necessary to place absorbent napkins under the head and on chest to ensure hygiene of the body and bed linen.
11. If possible, create conditions that remind the child of a “normal” meal: put cutlery in his hands, use a change of plates, etc.
12. When feeding with a spoon, use a chair to sit on, do not stand over the child, do not sit on the child's bed without his permission.
13. If the child refuses to eat, do not force-feed, if necessary, consult a nutritionist or pediatrician in a timely manner on dietary adjustments.
14. In children who maintain independent feeding and have a decreased chewing/swallowing speed, it is advisable to use homogeneous thick liquids (IDDSI level 4) [82].
15. When administering artificial nutrition, in order to optimize the speed and volume of the administered nutritional formula, among other things, the dynamics of intra-abdominal pressure should be taken into account [85].

EXCUSION FROM TUBE-FEEDING

After stabilization of the condition, restoration of nutritional status and effective breathing and swallowing, patients are transferred to independent feeding. In some cases, the transfer to oral feeding is postponed until transfer to a specialized department or until discharge from the hospital. H. Clouzeau et al. developed criteria for possible weaning from the tube [86, 87]:

1) stable course of the underlying disease;
2) absence of short- or medium-term planned interventions that may cause or increase the risk of nutritional deficiency;
3) satisfactory nutritional status in accordance with age-standard or disease-specific centile corridors, growth charts;
4) safe and functional swallowing;
5) readiness of health care staff and family.

When transferring a patient from artificial to independent feeding, it is extremely important to take into account the time of oral inactivity. Long-term artificial enteral feeding can lead to the formation of unwanted oral triggers (tube insertion procedure, reflux, vomiting, silent aspirations), lack of taste and texture sensations, disruption of parent-child interaction during feeding, and decreased appetite [87–89]. Several methods have been developed for weaning formula-fed infants [90, 91]. Some of these are based on a rapid reduction in caloric intake to induce hunger and wean patients off formula over several weeks during hospitalization under the supervision of health care workers [90].

FIMATHO and GFHGNP have published key recommendations for weaning children from tube feeding [86]. A multimodal strategy that combines caloric restriction with psychobehavioural and/or sensorimotor treatment is recommended. Psychological and behavioural characteristics of children and caregivers related to nutrition are considered in conjunction with cultural practices in psychological interventions [92]. Sensorimotor interventions based on afferentation or reafferentation of the oropharynx have been developed to correct tactile hypersensitivity. Restoration

of normal circadian rhythm is achieved using sensory oral stimulation even before switching to oral nutrition, during tube feeding. The acquisition of sucking, chewing and swallowing skills is achieved by oral motor interventions, which are divided into compensatory interventions (head turns and tilts, chin tucks, changes in viscosity, texture and volume of food), special exercises (tongue retention, neck flexion, supraglottic swallowing, supra-supraglottic swallowing, enhanced swallowing, Mendelsohn and Masako Maneuvers), alternative methods (passive gymnastics of the tongue, lips, vocal exercises). The criteria for effectiveness are jaw strength, lateral movements of the tongue, spiral movements of the lower jaw and sufficient lip tone.

CONCLUSION

Organization of enteral nutrition of children hospitalized in the intensive care unit is an important link in the multimodal therapeutic strategy. Providing enteral nutrition in accordance with the severity of the patient's condition, his ability to take food independently or to receive it with the help of special devices is the key to meeting the energy needs necessary for recovery. The developed scale for assessing the ability to independently eat FOIS and IDDSI allow for personalization of the therapy.

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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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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PRACTICAL ASPECTS OF ORGANIZATION OF ENTERAL NUTRITION IN PEDIATRIC INTENSIVE CARE UNIT PATIENTS. PART 2. TEXTURAL CHANGES AND FEATURES OF CARE DURING ENTERAL FEEDING

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ABSTRACT. Implementation of artificial nutrition in children hospitalized in intensive care unit (ICU) is an important task of the concept of multisystem organization of medical care. For enteral nutrition, taking into account contraindications or impossibility of independent feeding, food texture modifications are used. In case of swallowing disorders for various reasons, special devices — feeding tubes — are used to deliver the nutrient mixture. Implementation of care measures for feeding tubes and stomas allow to increase their service life while reducing the risk of various complications.

KEYWORDS: *textural changes of food, probe care, gastrostomy care, nutritional support, enteral nutrition in children*

ПРАКТИЧЕСКИЕ АСПЕКТЫ ОРГАНИЗАЦИИ ЭНТЕРАЛЬНОГО ПИТАНИЯ ПАЦИЕНТОВ ПЕДИАТРИЧЕСКИХ ОРИТ. ЧАСТЬ 2. ТЕКСТУРНЫЕ ИЗМЕНЕНИЯ И ОСОБЕННОСТИ УХОДА ПРИ ПРОВЕДЕНИИ ЭНТЕРАЛЬНОГО ПИТАНИЯ

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РЕЗЮМЕ. Проведение искусственного питания у детей, госпитализированных в отделение реанимации и интенсивной терапии (ОРИТ), является важной задачей концепции мультисистемной организации оказания медицинской помощи. Для энтерального питания, учитывая противопоказания или невозможность самостоятельного питания, применяются изменения текстуры пищи. При нарушениях глотания по различным причинам для доставки питательной смеси используются специальные устройства — питательные трубки. Осуществление мероприятий ухода за питательными зондами и стомами позволяет увеличить срок их эксплуатации при снижении риска различных осложнений.

КЛЮЧЕВЫЕ СЛОВА: *текстурные изменения пищи, уход за зондом, уход за гастростомой, нутритивная поддержка, энтеральное питание у детей*

INTRODUCTION

When administering enteral nutrition to patients with swallowing disorders, which include those hospitalized in intensive care units (ICU), it becomes necessary to change the texture of the nutritional formula [1–4]. The concept of "texture" takes into account the rheological and structural properties of food products, as well as the type of heat treatment. Largely determined by consistency, food texture is a broader concept determined by the patient using mechanical, tactile, visual and auditory receptors and allows one to characterize hardness, elasticity, stickiness, friability, viscosity and fluidity for liquids. Determining the consistency of food that a child can consume without the risk of aspiration is an important resource for early rehabilitation of ICU patients. The use of standardized scales, including the Functional oral intake scale (FOIS), allows to determine the necessary nutritional support strategy from the first day of hospitalization [5]. In children hospitalized in ICU, various technical devices are used to provide enteral nutrition in case of swallowing disorders or contraindications to independent feeding [6]. Most often, tubes (stomach or intestinal) are used, much less often nutritional stomas are used. General and special care measures for them allow for successful nutritional support, prevent the development of complications both in the early and late periods.

AIM

To demonstrate modern recommendations for the care of seriously ill children during artificial feeding.

FEATURES OF FOOD TEXTURE DURING ENTERAL NUTRITION

When prescribing enteral nutrition, it is important to choose right consistency of the formula while respecting its energy value. Liquid formulas are more convenient when administered through various tubes, while thick mixtures or mixtures thickened with special additives (locust bean gum, potato starch) can cause tube obstruction. If the patient is able to eat independently, depending on the functional status (2–7 levels on the Functional Oral Nutrition Scale — FOIS), it is necessary to individually select the consistency of food. In addition, the correct texture of the food bolus allows in some cases to prevent the development of aspiration in children with dysphagia of various origins, including that developed in the structure of the syndrome of consequences of intensive care [3, 7, 8]. Known differences in the processes of swallowing liquid and solid food allow choosing a specific food consistency for a specific patient [9–14]. To determine the texture of food, it is necessary to use developed tools that allow individualization of the prescription of nutritional support [9, 15–20]. One of the most convenient of these is the classification of modified food and liquid consistencies used in patients with dysphagia, proposed in 2017 (The International Dysphagia Diet Standardisation Initiative—IDDSI) (Fig. 1) [10, 20]. The use of the FOIS scale and the IDDSI system is becoming especially important in children hospitalized not only in ICU, but also when transferred to specialized departments, including in connection with the increase in the share of parental participation in the implementation of care measures.

According to the IDDSI classification, solid or semi-solid food that can be used in children with a formed act of chewing and swallowing corresponds to levels 5–7. As the levels decrease, the texture of the food becomes more pureed (6→3), and the liquid becomes less viscous (4→0), which is indicated by food manufacturers with color marking [12]. In addition, a syringe test is used to determine the 0–3 level of liquid, a spoon tilt test is used to determine the viscosity and stickiness of food at level 4, and a fork pressure test is used to assess food products at levels 4–7 (Table 1) [21]. The possibility of using the IDDSI system in assessing the nutrition of young children, including determining the degree of thickening of the formula, has been proven [22, 23].

The texture of normal food prepared using mechanical gentleness methods corresponds to level 7. Moreover, it may include a "double consistency" that simultaneously contains solid and liquid parts. It is prescribed to patients who can bite, chew for a long time, necessary to create a homogeneous food bolus, without experiencing pain and fatigue, and hold the food bolus in the oral cavity until swallowing. The assessment test can be performed with either a spoon or a fork. When

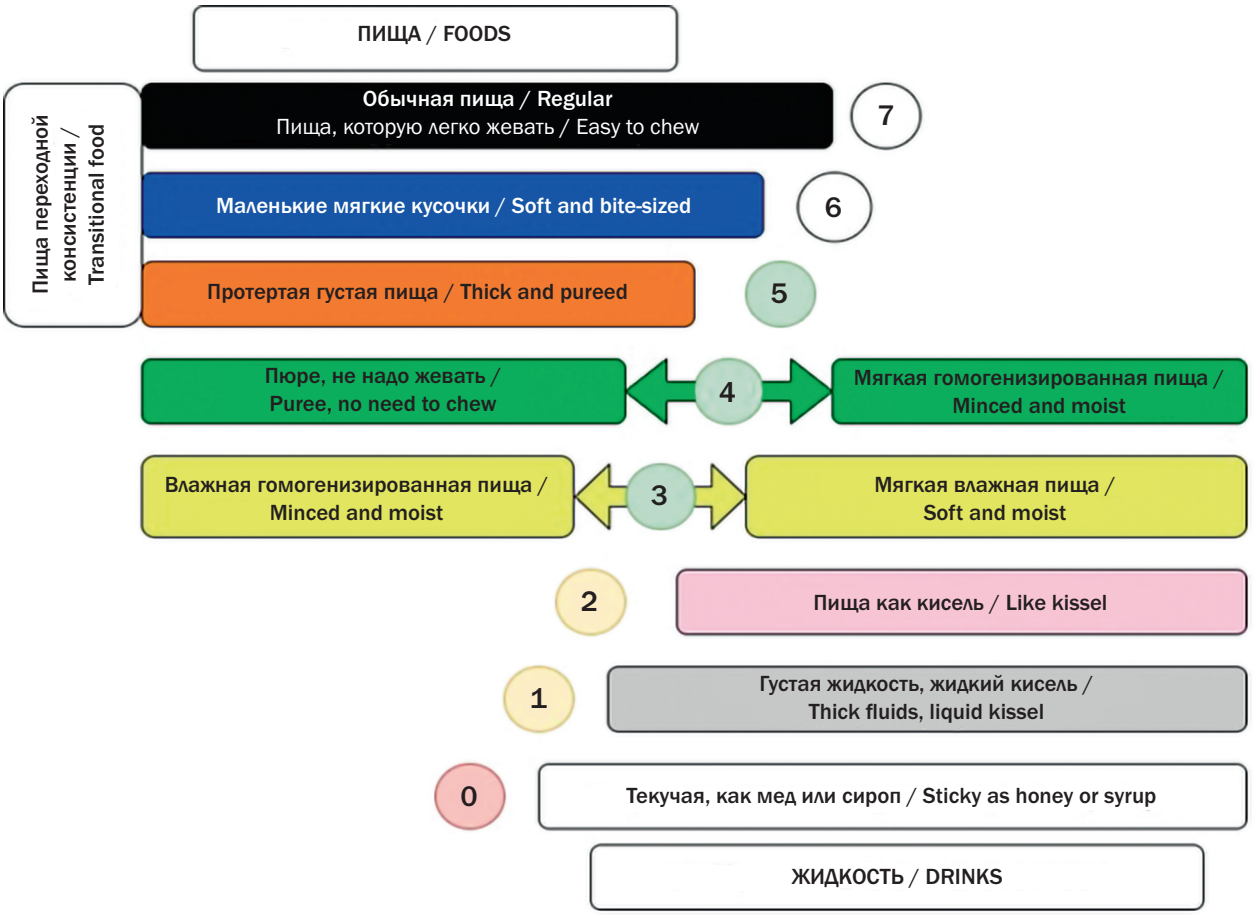
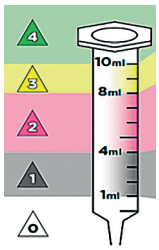
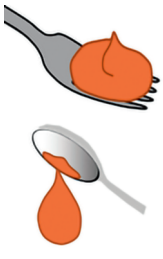
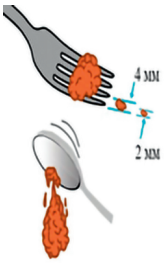
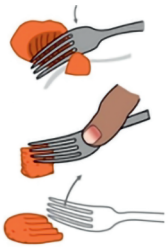


Fig. 1. Classification of modified food and liquid consistencies

Рис. 1. Классификация модифицированных консистенций пищи и жидкостей

Table 1. Levels of food and liquid consistencies [10]

Таблица 1. Классификация консистенции пищи и жидкостей [10]

Уровень / Level	0	1	2	3	4	5	6	7
Тест / Test								

performing the pressure test, a finger is pressed on a fork or spoon under a pressure of 17 kPa, which corresponds to the pressure of the tongue on food bolus during swallowing [10, 24, 25]. This is achieved by pressing the fork with a force that causes the nail plate to turn pale. Pieces of food smaller or larger than 8 mm for children under 5 years of age or 15 mm for children over 5 years of age and adults are used for the analysis [26]. After pressing, the food sample should lose its original shape without returning to its original shape after the end of the test.

Foods with a texture resembling soft pieces are classified as IDDSI level 6. These foods do not require biting, but chewing is required before swallowing.

Food samples may be crushed with a fork, spoon or chopsticks, with complete loss of the original texture. Chopped food corresponding to IDDSI level 5 is prescribed to patients who have the ability to chew minimally and swallow effectively. In this case, the chopping depends on age: for children under 5 years old, the length should not exceed 8 mm, and the width 2 mm, for children over 5 years old and adults, the length should not exceed 15 mm, the width 4 mm. In this case, the food lumps are easily separated from each other with the tongue. When pressing the fork with a finger with a force less than 17 kPa, the food lumps are easily separated and do not join together at the end of the test. The sample collected from the plate with a fork remains on it in the form of a slide, but can penetrate slightly through the teeth. When placing the sample on a spoon, the preservation of the structure of the food lumps is noted. When the spoon is tilted, the food easily "slides" down in a single lump. Puree foods or highly thickened liquids are IDDSI level 4. Such foods are eaten with a spoon or fork, but should not be drunk from a cup or with a straw. The food lump has a uniform, non-sticky consistency without lumps and does not require chewing. Under the influence of gravity (tilt of the spoon), it slowly flows down as a single lump, but does not pour, and when dropped, it retains its shape on the plate. A sample collected from the plate with a fork remains on it in the form of a slide, but a small amount may leak between the tines. When stored for a long time, the food does not separate into liquid and solid phases.

Liquid food is food with a consistency of 1–3 levels according to IDDSI. The evaluation uses a 10 ml syringe test into which the test sample is poured into the cylinder. In this case, the length of the syringe barrel at the 10 ml mark should be 61.5 mm. The amount remaining 10 seconds after opening the tip is estimated. If the remainder is 8 ml, level 3 according to IDDSI is set, 4–8 ml — level 2, 1–4 ml — level 1. Liquid remaining in a volume of less than 1 ml corresponds to the viscosity of water.

Liquid puréed food is IDDSI level 3. It can be drunk from a cup, but is difficult to drink through a 6.9 mm straw. The food does not hold its shape, and flows through the tines of a fork. Considering the consistency, the food does not require chewing and can be swallowed without first forming a bolus. Weakly thickened liquids, which are classified as level 2, can be drunk. Food does not hold its shape, flows quickly from a spoon, but more slowly than liquid of normal consistency. Requires little effort when drinking through a standard straw (diameter 5.3 mm). This consistency can be used in children with decreased muscle tone of the tongue. Level 1 is a slightly thickened liquid that passes freely through a standard tube, nipple on a bottle/cup. The consistency of the food resembles an industrially prepared formula for baby food of the "anti-reflux" type. It is used with a slight weakening of the swallowing reflex. Water, expressed breast milk, standard milk formula and liquids of similar consistency are classified as level 0 IDDSI. The liquid flows at the speed of water. You can drink from any cup and through straws of any diameter.

The choice of the optimal food texture is especially important in patients with swallowing disorders of various genesis. Depending on the severity of dysphagia, the preservation of independent swallowing, when deciding on maintaining oral nutrition, it is necessary to determine the type of food consistency that will lead to the lowest risk of aspiration and food retention in the laryngeal valleculae and pyriform sinuses. In all children before the introduction of complementary foods and in patients with severe dysphagia during artificial enteral feeding, it is necessary to use food texture levels 0–1 according to IDDSI. Thickening to levels 1–2 is possible in children with mild dysphagia with concomitant GERD when prescribing antireflux mixtures. Food texture levels 3–5 are allowed for children without swallowing disorders or conditions that prevent independent feeding, up to 1 year after the introduction of complementary foods, as well as for children with mild dysphagia. Consistency corresponding to food texture level 6 is prescribed to healthy children and children with mild dysphagia, mainly not associated with chewing disorders. Food level 7 is not prescribed for patients with dysphagia.

To support independent swallowing in a child requiring treatment in ICU, it is necessary to use various devices, in particular, special dishes and cutlery. The use of such products allows for increased swallowing safety. Examples of adapted dishes are modified nipples, cut-out cups, weighted spoons, angled spoons, sectio-

nal plates, and non-tipping bowls. Some studies show the benefits of carbonation of beverages in reducing the frequency and severity of aspiration in neurogenic dysphagia in children [27], who are often hospitalized in ICU due to nervous anorexia and developed water-electrolyte disorders.

Saliva, which is involved in the formation of a food bolus on the surface of the tongue before swallowing, is of great importance in maintaining independent nutrition. It has been proven that the rate of saliva production increases with the presence of food in the mouth and during chewing [28], while a decrease in saliva secretion (xerostomia) leads to a deterioration in the condition of the oral mucosa and a decrease in the quality of life of patients, including those hospitalized in ICU [29].

CONTROL OF RESIDUAL VOLUME OF THE STOMACH

The concept of gastric residual volume (GRV) monitoring before feeding is based on the prevention of nausea, vomiting, and aspiration in patients with gastroparesis, which is a common symptom in critically ill children [30, 31]. Studies have noted an increased risk of these complications when GRV reaches 5 ml/kg 3–4 hours after the last meal during continuous feeding or before each bolus feeding [31]. Currently, several studies have been conducted, which have provided conflicting data on the value of this method [30, 32, 33]. Z. Wang et al. (2019) did not reveal an increase in the incidence of aspiration, ventilator-associated pneumonia, or the development of feeding intolerance in the absence of gastric residual volume monitoring [34].

Obtaining results depends on a number of factors, including the size of the syringe, the pressure used for aspiration, the viscosity of the aspirated fluid, the material and size of the gastric tube, and the location of the distal end of the tube [35, 36]. The use of small syringes results in the creation of less negative pressure, which leads to distortion of the results. The walls of silicone tubes are compressed during active aspiration, which also leads to false negative results in determining GRV [31]. At the same time, the positive aspects of aspiration include the ability to control the nature of the contents (blood, bile, gastric or intestinal discharge), which allows for timely diagnosis of the development of complications [31].

Further studies are needed to determine the role of ultrasound in assessing GRV in pediatric ICU patients as a bedside diagnostic tool [37].

CARE OF NUTRITION TUBES

The list of possible special care measures for feeding tubes is huge and includes all stages, from insertion of the tube to its removal. The manipulations should ensure not only the physical well-being of the patient, but also the psychological one. Lack of control over the implementation of care measures for tubes can lead to the development of various complications (Table 2). When directly feeding the child, certain requirements must be observed. Taking into account the constant opening of the esophageal sphincters, to prevent passive aspiration after the introduction of a nutritional mixture during bolus feeding, it is necessary to leave the child, in the absence of contraindications, in a semi-sitting position for 30–40 min. The development of emetic syndrome should be diagnosed in a timely manner with temporary cessation of the introduction of the formula, prescription of antiemetic drugs. In case of relapses of nausea and vomiting, the rate or volume of the introduced nutritional mixture is reduced. Considering the frequent placement of the distal section of the tube in the postpyloric region, after taking food and medications, the tube should be rinsed with water to prevent obstruction of the lumen, and if there are difficulties with the introduction of formula, the tube should be rinsed with water, and if ineffective, with a carbonated drink or an aqueous solution of pancreatin [6, 38]. If it is impossible to restore the tube's patency, it should be removed and replaced with a new one. With prolonged use of nasogastric tubes (more than 1–3 weeks), it is recommended to change the nasal passages to prevent trophic disorders.

Great attention must be paid to fixing the tube to prevent its displacement, completely cleaning the syringe during repeated use, and also to control the rate of administration of the mixture, since these aspects are most often not performed during feeding [39].

Table 2. Complications of gastric tube placement

Таблица 2. Осложнения постановки желудочного зонда

Частые осложнения / Frequent complications	**Редкие осложнения / Rare complications**
Интубация трахеи, аспирационная пневмония [40, 41] / Tracheal intubation, aspiration pneumonia	Перфорация пищевода [42] или желудка [43] / Perforation of the esophagus or stomach
Гастроэзофагеальный рефлюкс при постонно открытом нижнем пищеводном сфинктере / Gastroesophageal reflux in postonally open lower esophageal sphincter	Гидропневмоторакс [44] и гидропневмоперитонеум [45] / Hydropneumothorax and hydropneumoperitoneum
Транспилорическая транслокация с развитием демпинг-синдрома / Transesophageal translocation with development of dumping syndrome	Стеноз пищевода / Esophageal stenosis
Перекручивание, завязывание узла / Torsion, knotting	Перфорация решетчатого лабиринта / Perforation of the lattice labyrinth
Носовые кровотечения при постановке / Nasal bleeding during probe placement	Постановка в головной или спинной мозг при переломе основания черепа / Placement in the brain or spinal cord during skull base fracture
Отек слизистой оболочки носоглотки / Edema of nasopharyngeal mucosa	Эзофагит / Esophagitis
Риносинуситы / Rhinosinusitis	Пролежни / Bedsores
Отиты при длительном нахождении зонда / Otitis media with prolonged probe placement	Кариес, орофарингеальный кандидоз / Caries, oropharyngeal candidiasis

ORGANIZATION OF NUTRITION THROUGH NUTRITIONAL STOMATS

Gastrostomy tubes are installed in children hospitalized in ICU for a long time. Although not a physiological route for delivering nutrients, nutritional support through nutritional stomas allows for the satisfaction of patients' energy needs [46]. When organizing care measures, it is necessary to remember the possibility of developing early and late complications. In the presence of a gastrostomy, all complications can be divided by the time of occurrence (Table 3) [47–51].

In order to prevent infectious complications, it is necessary to change dressings daily [53]. In case of defective care and failure to observe asepsis when working with a postoperative wound, infectious complications arise: abscess, cellulitis, necrotizing fasciitis. The most common sources are bacterial (*Staphylococcus aureus, Pseudomonas, Escherichia coli, Enterobacter cloacae, Streptococcus, Lactobacillus and Bacteroides*) or fungal (*Candida* spp.) flora. Healthcare-associated infections are of particular importance. To prevent them, it is necessary to carry out daily dressings of the stoma area with fixation of aseptic dressings with a Y-shaped incision until the wound is completely healed. If hyperemia, pain, exudate appear, a bacteriological study of the wound discharge is carried out, systemic antimicrobial and antifungal therapy is prescribed. In the absence of positive dynamics against the background of conservative therapy, and the detection of fasciitis, surgical intervention is indicated.

The gastrostomy tube affects the change in the microbiome of the stomach and the entire digestive tract [54, 55]. A decrease in the α-diversity of microorganisms (a decrease in the Shannon index), a reduction in Firmicutes-type bacteria and an increase in *Bacteroides* have been shown. At the same time, a decrease in the *Firmicutes / Bacteroides* index is associated with an increase in the duration of hospitalization in ICU and the likelihood of an unfavorable outcome [55, 56].

After complete healing of the wound, it is necessary to change the position of the gastrostomy tube by 180–360°, and also move it up and down (deep) by approximately 1–2 cm to prevent the growth of granulation [38]. To prevent obstruction of the lumen of

Table 3. Postoperative complications after gastrostomy

Таблица 3. Послеоперационные осложнения после гастростомии

Ранние осложнения (менее 72–96 часов) / Early complications (less than 72–96 hours)	**Поздние осложнения (более 72–96 часов) / Late complications (more than 72–96 hours)**	**Отсроченные осложнения (более 1 месяца) / Delayed complications (more than 1 month)**	**Вне зависимости от времени / Regardless of time**
Абсцесс или целлюлит брюшной стенки / Abdominal wall abscess or cellulitis		Постпилорическая миграция / Postpyloric migration	Засорение трубки / Tube blockage
Чреспеченочное размещение / Transhepatic placement	Пневмоперитонеум / Pneumoperitoneum	Грануляции / Granulations	Внутрибрюшинное истечение желудочного содержимого / Intraperitoneal effusion of gastric contents
Кровотечение из желудочных артерий / Bleeding from gastric arteries	Расхождение краев ран, эвентрация / Wound margin separation, euteration	Демпинг-синдромом / Dumping syndrome	Перистомальная инфекция / Peristomal infection
Гемоперитонеум / Hemoperitoneum	Контактный дерматит / Contact dermatitis	Бампер-синдром [52] / Bumper syndrome	Аспирационная пневмония / Aspiration pneumonia
Постнаркозные осложнения / Post anesthesia complications			Перфорация желудка / Gastric perforation
			Незапланированное удаление трубки / Unplanned tube removal

the tube, it is necessary to correlate the diameter with formula's consistency (according to IDDSI no more than 0–3).

When there is excessive compression of tissue between the external and internal fixation devices of the gastrostomy tube, bumper syndrome occurs, characterized by ischemia, necrosis and infection of soft tissues [52]. In this case, the bumper can be at any distance between the gastric mucosa and the skin, which can lead to gastric perforation, peritonitis, and subcutaneous fat infections. A characteristic triad of symptoms is described: the inability to administer the mixture, obstruction of the tube, and leakage of gastric contents into the stoma area. To prevent this syndrome, it is necessary to ensure the correct positioning of the external cushion between the skin and the external fixator, which should be at least 10 mm. A positive effect is provided by weekly changes in the tube position by 180–360° after unfastening the external fixing plate (after the wound has healed). When bumper syndrome develops, surgical intervention with reinstallation of the tube is indicated.

If the gastrostomy is not sufficiently fixed to the skin, as well as if there is active gastrointestinal peristalsis, the intragastric balloon may be dislocated beyond the pyloric sphincter. Against this background, nausea, vomiting (especially during feeding), and hypoglycemia often develop. In severe cases, dumping syndrome develops. To prevent complications, it is necessary to apply a mark on the outer part of the gastrostomy tube as a reference point and, if necessary, tighten the tube. In case of frequent relapses, the issue of installing a low-profile gastrostomy should be considered.

Excessive traction of the gastrostomy tube or trauma leads to the growth of granulation tissue, which may cause a loose fit of the pressure plate with leakage of gastric contents or dislocation of the tube. In addition, the appearance of granulation leads to difficulty in implementing care measures with subsequent development of infectious complications.

Frequent movements of a gastrostomy tube, proliferation of granulation tissue, decreased motility of the gastrointestinal tract, severe coughing leading to

increased intra-abdominal pressure, and cracks in the tube itself lead to leakage of acidic gastric contents from the stoma. This not only increases the diameter of the stoma, but also damages the skin with the development of contact dermatitis. To prevent excessive mobility of the tube, it is recommended to attach it to the skin of the anterior abdominal wall, and not to clothing. Avoid pulling or bending the tube too tightly. Check the balloon for water at least once a week to ensure it is filled to the volume recommended by the doctor. If there are no contraindications, medications that reduce stomach acidity are prescribed. In case of problems with intestinal peristalsis, gastrostasis, pharmacological correction is also carried out. In case of development of contact dermatitis, it is necessary to use protective cream, petroleum jelly or zinc paste. In some cases, it is recommended to remove the gastrostomy tube for a short period to stimulate narrowing of the lumen. To prevent stenosis of the gastrostomy, tubes of a smaller diameter are inserted into the lumen or, if absent, a Foley catheter with subsequent inflation of the balloon.

Thickening of the formula, deposition of lumps or medications can lead to narrowing of the lumen and obstruction of the gastrostomy tube. In this case, it is technically impossible to introduce the nutritional mixture or medications. To prevent complications, it is necessary to flush the gastrostomy tube with warm water before and after the introduction of nutritional formula and medications. For children receiving continuous enteral feeding, the tube should be flushed every 4–6 hours. To prevent drug deposits due to incomplete dissolution of solid forms, solution analogues are used whenever possible. The blocked tubes are immediately washed with carbonated water using a syringe, then the contents are aspirated with a syringe, pancreatic enzymes may be used. The absence of a positive effect from the conservative therapy determines the indications for surgical intervention with reimplantation of the gastrostomy.

The algorithm for care of the postoperative wound and gastrostomy in children (adapted from Wiernicka A. et al., 2016) [57] is as follows.

Day 1:

- First dressing change in the morning after gastrostomy placement.
- Inspect the wound to determine early complications (bleeding, erythema, discharge, induration, allergic skin reaction, etc.).
- Insert the tube 1–3 cm (depending on the child's age) ventrally and gently pull it back until the internal fixation flange resists.
- Place a Y-shaped aseptic dressing under the tube.
- The external fixation plate is secured with free movement of at least 5 mm.

Days 2–7

- Change dressings daily, inspecting the wound to detect complications.
- Finish dressings by fixing aseptic dressings.
- Attach the outer part of the gastrostomy tube to the child's skin (not to clothing) to prevent accidental removal during clothing changes.

7–14 days

Dressings can be changed once every 2–3 days depending on contamination.

Regularly inspect the wound to detect late, delayed complications.

Patients' hygiene (washing with soap and water or taking a shower) is performed after the initial healing of the postoperative wound [58].

ORAL CARE

In cases of swallowing disorder, especially in intubated patients on mechanical ventilation, bacterial colonization is observed in the oropharynx. Risk factors include the use of certain medications, lack of oral food or liquid intake, and dry mouth [59].

Mechanical cleaning of teeth is carried out mainly with a toothbrush. In conscious patients, accessible to productive contact, electric toothbrushes can be used to increase the effectiveness of cleaning. In any case, brushing teeth should be aimed at areas where plaque and food debris accumulate (around the gums and fissures on the chewing surfaces of the teeth). Brushing teeth should be done carefully, using a toothbrush with a small head and soft bristles, which helps avoid accidental injury to the gums, at least 2 times a day, and after each meal, for at least 1–2 minutes. It is necessary to clean all surfaces of the teeth and, if possible, soft tissues. To clean the interdental space, it is necessary to use dental floss, as well as special solutions for rinsing (if the swallowing re-

flex is preserved). If there is no possibility for mechanical cleaning of the oral cavity with a toothbrush, it is necessary to use gauze swabs moistened with a solution of an aqueous antiseptic, for example, chlorhexidine. To remove food debris, you can use rinsing with subsequent or simultaneous aspiration with an electric suction device.

To reduce the risk of dental caries, mechanical cleaning with a toothbrush should be supplemented with methods of remineralization of the tooth structure. Methods of maintaining hydration of the oral mucosa, diet modification, and the use of special pastes enriched with fluoride are used. The inclusion of fluorides in the crystalline structure of tooth enamel reduces the pH at which it dissolves.

CONCLUSION

Organization of nutritional support in patients hospitalized in ICU is a complex process that requires an individual approach to the choice of food consistency, feeding method, and care of feeding tubes during artificial nutrition. Optimization of food texture in patients with dysphagia and changes in feeding methods helps to prevent complications, while routine measurement of residual gastric volume during nutritional support does not reduce the incidence of aspiration and manifestations of emetic syndrome.

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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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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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. Работа выполнена в рамках НИР (номер госучета НИОКТР AAAA-A18-118113090077-0 от 30.11.18) «Скрининг нутритивного статуса у детей с соматической, хирургической и неврологической патологией, возможности коррекции».

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CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF POLIO AT THE PRESENT STAGE (LITERATURE REVIEW)

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ABSTRACT. ***Introduction.*** According to the World Health Organization (WHO), in a number of regions endemic for poliomyelitis there are cases of various forms of poliomyelitis associated with the continued circulation of vaccine-derived polioviruses and an unfavorable social and epidemiological situation. In the Russian Federation (RF), the situation is assessed as favorable, but there is a high risk of poliomyelitis cases occurring in neighboring countries (Tajikistan, Ukraine), which raises serious concerns due to the growing possibility of importation of wild strains and circulating vaccine-derived polioviruses (cVDPV). It is impossible to exclude the emergence of local cVDPV in the territory of the Russian Federation and the occurrence of new cases of vaccine-associated paralytic poliomyelitis (VAPP) if sanitary rules and regulations are not observed. ***Purposes and tasks*** — to study the clinical and epidemiological aspects of polio at the present stage. ***Materials and methods.*** Russian-language and foreign literary sources, processing, analysis and visualization of information. ***Results.*** To date, two states — Afghanistan, Pakistan — are endemic for wild poliovirus type 1. In 2021–2022, cases of importation of wild poliovirus type 1 to Malawi and Mozambique were reported. In 2024, 6 confirmed cases of polio caused by the wild strain were identified in these States. The problem of circulating vaccine strains of type 2 also remains relevant. In 2022, these viruses were detected in wastewater from London, New York and Jerusalem. According to WHO, for 2023 there are 308 cases of polio caused by mutated type 2 vaccine poliovirus worldwide. Since 2021, a new stable monovalent oral polio vaccine (nOPV2) containing a more. genetically stable type 2 vaccine poliovirus has been certified.

KEYWORDS: *epidemiology, vaccine-associated paralytic poliomyelitis, type 1 wild poliovirus, circulating vaccine-derived poliovirus 2 type, immunoprophylaxis*

КЛИНИКО-ЭПИДЕМИОЛОГИЧЕСКИЕ АСПЕКТЫ ПОЛИОМИЕЛИТА НА СОВРЕМЕННОМ ЭТАПЕ (ОБЗОР ЛИТЕРАТУРЫ)

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РЕЗЮМЕ. ***Введение.*** По данным Всемирной организации здравоохранения (ВОЗ), в ряде эндемичных по полиомиелиту регионах встречаются случаи заболевания различными формами полиомиелита, связанные с сохранением циркуляции полиовирусов вакцинального происхождения и с неблагоприятной социальной и эпидемиологической обстановкой. В Российской Федерации (РФ) ситуация оценивается как благополучная, но имеют место высокие риски возникновения случаев полиомиелита на территории близлежащих государств (Таджикистан, Украина), что вызывает серьезные опасения в связи с растущей возможностью завоза диких штаммов и циркулирующих полиовирусов вакцинного происхождения (цПВВП). Невозможно исключить появление локальных цПВВП на территории РФ и возникновение новых случаев вакцин-ассоциированного паралитического полиомиелита (ВАПП) при несоблюдении санитарных правил и норм. ***Цель*** — изучить клинико-эпидемиологические аспекты полиомиелита на современном этапе. ***Материалы и методы.*** Русскоязычные и иностранные литературные источники, обработка, анализ и визуализация информации. ***Результаты.*** В настоящее время эндемичными по дикому полиовирусу 1-го типа являются два государства — Афганистан и Пакистан. В 2021–2022 гг. зарегистрированы случаи завоза дикого полиовируса 1-го типа в Малави и Мозамбик. В 2024 г. выявлено 6 подтвержденных случаев полиомиелита, вызванных диким штаммом в этих государствах. Актуальность сохраняет также проблема циркулирующих вакцинных штаммов 2-го типа. В 2022 г. эти вирусы обнаруживались в сточных водах Лондона, Нью-Йорка и Иерусалима. По данным ВОЗ, за 2023 г. в мире зарегистрировано 308 случаев полиомиелита, вызванного мутировавшим вакцинным полиовирусом 2-го типа. С 2021 г. сертифицирована новая стабильная моновалентная оральная полиомиелитная вакцина (nOPV2), содержащая более генетически стабильный вакцинный полиовирус 2-го типа.

КЛЮЧЕВЫЕ СЛОВА: *эпидемиология, вакцин-ассоциированный паралитический полиомиелит, дикий полиовирус 1-го типа, циркулирующий полиовирус вакцинного происхождения 2-го типа, иммунопрофилактика*

INTRODUCTION

According to the World Health Organization (WHO), against the backdrop of the pandemic of a new coronavirus infection, military conflicts, unfavorable epidemiological situation in regions endemic for poliomyelitis, unjustified vaccine refusals, non-compliance with vaccination schedules in Third World countries, and the continued circulation of vaccine-derived polioviruses, the incidence of various forms of polio remains [1–4].

In the Russian Federation (RF), the polio situation is assessed as favorable, but there is a high risk of cases of the disease occurring in neighboring countries (Tajikistan, Ukraine). This raises serious concerns due to the growing possibility of importation of wild strains and circulating vaccine-derived polioviruses (cVDPV). It is impossible to exclude the emergence of local cVDPV in the RF and the occurrence of new cases of vaccine-associated paralytic poliomyelitis (VAPP) if sanitary vaccination standards are not observed [5, 6].

In 2022, new cases of wild poliovirus (WPV) type 1 were documented in countries declared polio-free. cVDPV types 2 and 3 were reported in waste waters in New York City and Jerusalem. Environmental surveillance sequencing showed that cVDPV type 2 strains from New York and Jerusalem were related not only to each other but also to environmental isolates found in London [7]. In the United States, a case of paralytic poliomyelitis caused by cVDPV type 2 was reported on 18 July 2022 in an unvaccinated patient with immunodeficiency [8].

The Global Polio Eradication Initiative has made significant progress. According to WHO, two out of three strains of wild poliovirus have now been eradicated worldwide. The WHO regions: Africa, Americas, Europe, Eastern Mediterranean and Western Pacific are certified polio-free. Endemic transmission of wild poliovirus type 1 persists in Afghanistan and Pakistan, where 12 cases of polio caused by WPV type 1 were reported in 2023. Additional surveillance in 2023, such as wastewater monitoring, shows widespread circulation of wild poliovirus type 1 among the population in endemic countries. This poses risks of international spread due to population migration [5].

According to the WHO, the new polio eradication strategy is planned to allocate from 4.5 to 6.2 billion dollars annually [9].

The causative agent of polio is *Poliovirus hominis*, which belongs to the family *Picornaviriadae*, the genus *Enterovirus*. It is an RNA + virus, the genome of which is about 7500 nucleotides long, size is 7.4 kb. The virus has an icosahedral capsid measuring 30 nm, consisting of 60 copies of 4 structural proteins (VP1, VP2, VP3, VP4). The genome contains a large open reading frame, framed by a highly structured 5'-untranslated region, ending with a poly(A) tail. The open reading frame encodes a polyprotein that is cleaved into four capsid proteins and seven non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, and 3D) involved in viral replication. The second, shorter reading frame encodes the ORF2p protein, which plays a significant role in viral replication [10–12].

There are three serotypes of wild poliovirus: type 1 — Brunhilde, it is characterized by epidemic outbreaks with the development of paralysis; type 2 — Lansing, the causative agent of sporadic cases; type 3 — Leon, causes VAPP. Since 1999, no case of wild poliovirus type 2 has been registered in the RF, and since 2012 — type 3 [13].

The pathogenesis of poliomyelitis is characterized by four phases: enteric, lymphogenous, viremic, and neural. The enteric phase is characterized by the entry of wild poliovirus into the gastrointestinal tract [14], after which the virus attaches to the CD155 receptors of epithelial cells. This causes conformational changes in the viral capsid necessary for the release of viral RNA into the cell cytoplasm [11]. During the lymphogenous phase, WPV replicates in the lymph nodes of the small intestine and Peyer's patches. Then, in the viremic phase, the virus enters the bloodstream. This leads to dissemination and replication in organs and tissues: spleen, liver, lungs, myocardium. The development of latent and abortive forms of the disease is associated with this stage of pathogenesis. Virus replication is also possible in muscle tissue, which causes myalgia before paralysis. In the neural phase, poliovirus enters the central nervous system through the blood-brain barrier. There is another variant of virus spreading — perineural. It consists of the entry of the infectious agent through the autonomic fibers of

the nerves innervating the gastrointestinal tract into the segments of the spinal cord. Poliovirus affects the gray matter of the spinal cord and brainstem, mainly the motor neurons of the anterior horns of the spinal cord, the motor nuclei of the cranial nerves (glossopharyngeal, vagus, facial, etc.). It is characterized by mosaic pattern and asymmetry of damage to individual muscle groups. In some cases, neurons of the posterior horns, cells of the spinal ganglia can be affected. The midbrain, cerebellar nuclei and cerebral cortex (neurons of the moto region of the frontal lobe of the cerebral cortex) can be affected in the brain. The posterior roots of the spinal cord are rarely involved in the inflammatory process, so there are no sensory disturbances in polio patients. Sometimes the reticular formation is affected. The presence of pain syndrome and neural tension symptoms is associated with damage to the spinal meninges [14]. It is worth noting that poliovirus does not replicate in muscles in vivo. All changes occurring in peripheral nerves and skeletal muscles are secondary to the neuronal cell death [15].

Strains included in the oral poliovirus vaccine (OPV) can mutate and become cVDPV, causing polio cases in regions with low immunization rates [12]. This is due to the lack of proofreading ability in RNA-dependent RNA polymerase, which leads to point mutations in the viral genome. This results in the formation of cVDPV types 1, 2, and 3 [10]. In addition to mutations, vaccine strains of polioviruses are capable of recombination with other enteroviruses C in coinfections and the return pathogenic properties [2]. One nucleotide site that is critical for attenuation lies in the 5' non-coding region of the genome of each of the three OPV strains, at nucleotide 480 in type 1, 481 in type 2 and 472 in type 3. Two mechanisms can lead to the formation of chimeric genes. The first is “break-and-join” mechanism, in which the genetic sequence of one parental genome is cleaved by a nuclease and re-ligated with a sequence derived from the other parental genome. The second is “copy-choice” mechanism, in which a nascent RNA strand switches the template strand during genome replication. It is these processes at the nucleotide sites of attenuation that lead to the adaptation of vaccine strains of polioviruses and the acquisition of pathogenic properties [16].

Currently, the WHO strategy has introduced novel oral polio vaccine type 2 (nOPV2) [9] as of 2021. Since March 2021, approximately 450 million doses of this vaccine have been distributed for local use to control cVDPV type 2 cases in 21 countries [17]. Modifications to the poliovirus genome in this vaccine stabilize mutations in the 5’-untranslated region, suppress replication with other enterovirus types in coinfections, and limit the adaptability of the virus [18].

EPIDEMIOLOGICAL SITUATION IN REGIONS OF THE WORLD ENDEMIC FOR WILD POLIOVIRUS TYPE 1

Currently, Pakistan and Afghanistan remain endemic countries for poliomyelitis (according to WHO data). The dynamics of polio cases caused by wild poliovirus type 1 are presented in Figure 1. The maximum rates were observed in 2019–2020, a decrease was noted in 2021 and an increase in 2022. In 2024, after the data update on 28.05.2024, 6 confirmed polio cases caused by WPV type 1 were detected in endemic countries. The last cases were detected in April 2024 [19].

The dynamics of the number of isolated WPV type 1 strains from the environment in endemic regions is shown in Figure 2. The maximum values were observed in 2019–2020, a decrease was noted by 2021 and an increase in 2023. In 2024, after updating WHO data on 05.28.2024, 173 isolated WPV type 1 strains were detected from the environment. In 2021–2022, importation into countries declared polio-free was registered — Malawi and Mozambique [19].

In Afghanistan, the unfavorable epidemiological situation has developed due to the ban on house-to-house polio vaccinations. This has led to the fact that since May 2018, more than 1 million children in the southern regions of the country have been systematically not covered by immunization against polio. As a result, in 2019–2020, 90% and 75% of polio cases caused by WPV type 1 in Afghanistan, respectively, occurred in areas currently inaccessible for vaccination. In areas accessible for vaccination, there are personnel problems, and there are no accounting and reporting mechanisms [9].

Fig. 1. The dynamics of the incidence of polio caused by type 1 wild poliovirus in endemic regions

Рис. 1. Динамика заболеваемости полиомиелитом, вызванным диким полиовирусом 1-го типа, в эндемичных регионах мира

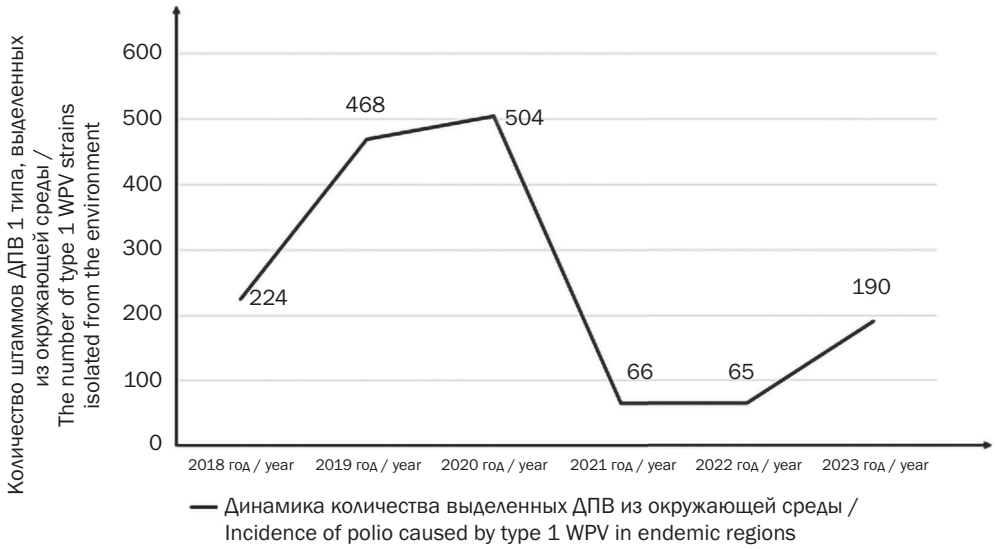

Fig. 2. Dynamics of the number of isolated wild poliovirus (WPV) type 1 strains from the environment in endemic regions

Рис. 2. Динамика количества выделенных штаммов диких полиовирусов (ДПВ) 1-го типа из окружающей среды в эндемичных регионах мира

In Pakistan, progress has been hampered by a combination of factors: decreased vigilance against a declining incidence from 2015 to mid-2018; no new cases were reported for several months; a change in national leadership; increasing public distrust of vaccines; discrepancy between emerging issues and traditional vaccine approaches. The growing amount of information on social networks from supporters of the anti-vaccination movement contributes to an increase in the frequency of unjustified refusals of parents to vaccinate. Immunization coverage has been impacted by a lack of effective engagement with special populations at high risk of polio, particularly the Pashtuns, who make up 15% of the country's population. Despite

the small size of this social group, it accounts for 81% of polio cases caused by WPV type 1 in Pakistan over the past 10 years [9].

In these countries, the previously mentioned problems have been exacerbated by the COVID-19 pandemic. In early 2020, the first wave of COVID-19 led to restrictions on movement and the temporary suspension of polio activities between March and July. During this pause, surveillance quality deteriorated and immunization campaigns were postponed. In 2021 and beyond, the introduction of COVID-19 vaccines has presented an opportunity to conduct public health education work among the population on immunoprophylaxis, including against polio [9].

EPIDEMIOLOGICAL SITUATION IN REGIONS OF THE WORLD WITH CIRCULATING VACCINE-DERIVED POLIOVIRUS

According to WHO, in addition to WPV type 1, cVDPV type 2 mainly continues to circulate in Africa and endemic countries. Elimination of WPV type 2 was declared in 2015. Following this, in April 2016, a global switch from trivalent to bivalent OPV containing poliovirus types 1 and 3 was implemented to completely eliminate the use of live attenuated vaccine type 2 and its associated risks. Outbreaks associated with cVDPV type 2 have emerged, despite the fact that this was preceded by the introduction of one dose of inactivated polio vaccine (IPV) in national immunization schedules and enhanced measures to increase herd immunity to vaccine-derived poliovirus type 2. Delay in measures taken in a number of African countries led to the emergence of a non-immune layer of the population group to poliovirus type 2 [20]. From 2016 to 2020, 64 cVDPV type 2 outbreaks have been reported, affecting 33 countries and causing a total of 1,572 cases of paralytic polio. In 2020, 1,082 cases of cVDPV type 2 infection were detected in 29 countries, 14 of which affected for the first time. The increase in cases is due to large outbreaks in countries such as Afghanistan, Pakistan, Chad, and Côte d'Ivoire, which together accounted for 59% of the total cases reported in 2020. The COVID-19-related pause in polio control activities from March to July 2020, in combination with disruptions basic immunization and IPV vaccination, also led to increased transmission of viruses. In early 2021, the risks associated with the spread of ongoing cVDPV type 2 outbreaks increased as these outbreaks threatened large population groups that lack immunity to cVDPV type 2 [9]. The dynamics of the number of polio cases worldwide

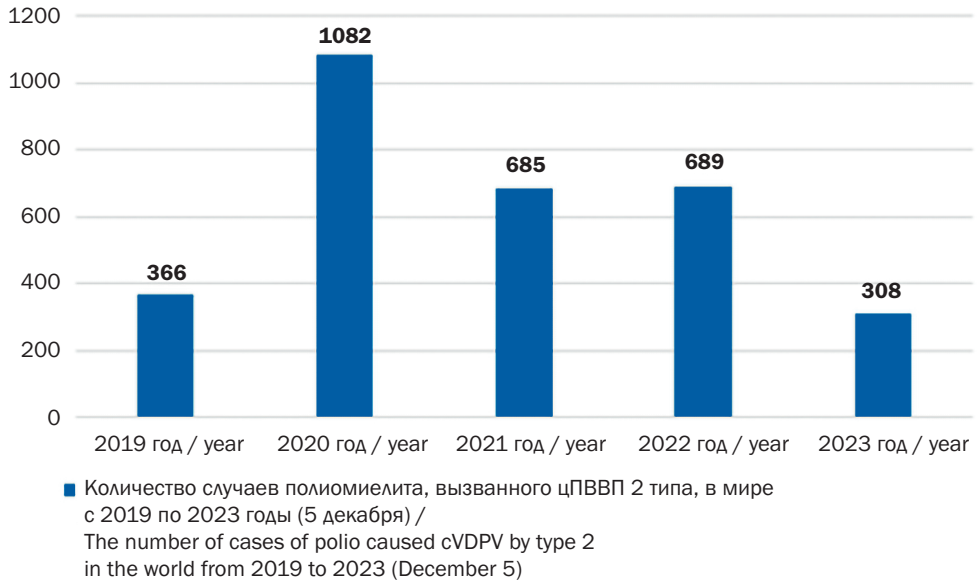

Fig. 3. Dynamics of the number of polio cases caused by type 2 circulating vaccine-derived polioviruses (cVDPV) in world (2019–2023 years)

Рис. 3. Динамика количества случаев полиомиелита в мире, вызванных циркулирующими полиовирусами вакцинного происхождения (цПВВП) 2-го типа (2019–2023 гг.)

caused by cVDPV type 2 from 2019 to 5 December 2023 is shown in Figure 3 [20].

The spread and continuation of cVDPV type 2 outbreaks are due to several factors: decreased mucosal immunity to cVDPV type 2 among young children born after the switch from trivalent to bivalent OPV; low coverage of basic IPV immunization; population migration, which allows the virus to be transmitted from one population to another; late detection of cVDPV type 2 outbreaks; delayed response to outbreaks; insufficient coverage of supplementary immunization measures [9].

IMMUNIZATION ACTIVITIES IN ENDEMIC REGIONS OF THE WORLD

WHO and UNICEF (an international organization operating under the auspices of the United Nations) estimate that national childhood coverage in Pakistan with three doses of OPV and one dose of IPV at 12 months of age was 83% for each vaccine in 2021. A 2021 study by C. Mbaeyi et al., supported by Gavi, the Vaccine Alliance, indicated that the proportion of children aged 12–23 months who had received 3 routine immunization OPV doses ranged by province from 45.1% in Balochistan to 94.9% in Punjab. None of the districts in the provinces of Balochistan, Khyber Pakhtunkhwa, and Sindh had coverage greater than 80%, compared with 31 (86%) of 36 districts in Punjab province [21].

Pakistan has also implemented supplementary immunization activities in response to cVDPV2 outbreaks using trivalent and nOPV2. In 2022, two national immunization days were conducted, targeting 44 million children under 5 years of age and five subnational immunization days for smaller populations. In 2023, one national immunization event and four subnational immunization events (February, March, May, and June) were held from January 2022 to June 2023, according to C. Mbaeyi et al. There are approximately 1.1 million children under 5 years of age eligible for vaccination in seven southern districts of Khyber Pakhtunkhwa. About 50,000 children in the region regularly miss out on OPV immunization, including 19,500 children in South Waziristan. In that district, militants have intimidated local health workers and prevented them from vaccinating children since August 2022, resulting in 19,500 children not receiving the vaccine. In January 2023, 505,750 children eligible for immunization were not vaccinated in the country, including 22,466 (4%) refusals [21, 22].

According to the WHO and UNICEF estimates, national coverage with three doses of OPV among children aged 12–23 months in Afghanistan was 71% in 2021 and 76% in 2022. Coverage with one dose of IPV in Afghanistan was 67% in 2021 and 71% in 2022. During 2023, routine immunization coverage with three doses or less of OPV increased to 73%, and the proportion of children who did not receive OPV decreased to 13%. The proportion of infants and children who never received OPV decreased from 1.4% in 2022 to 0.8% in 2023. In addition to routine immunization, Afghanistan offers vaccination to children under 10 years of age on major travel routes throughout the country and to persons of all ages at two border crossing points with Pakistan. During January 2022–June 2023, a total of 14,106,879 doses of bivalent OPV were administered at transit points and 1,690,497 at border crossings. Afghanistan also conducts regular surveillance for cases of acute flaccid paralysis, as one of the causes may be poliovirus [23].

CLINICAL AND EPIDEMIOLOGICAL SITUATION OF POLIO IN THE RUSSIAN FEDERATION

The Russian Federation has maintained its status as a polio-free country since 2002. The polio situation is assessed as favorable, but there remains a high risk of cases occurring in neighboring countries (Tajikistan, Ukraine). This raises serious concerns due to the growing possibility of importation of wild strains and circulating vaccine-derived polioviruses (cVDPVs). It is impossible to exclude the risk of the emergence of local cVDPVs in the RF and occurrence of new cases of vaccine-associated paralytic poliomyelitis if sanitary vaccination standards are not observed [5, 6, 24].

VAPP remains relevant in the RF. The dynamics of cases of vaccine-associated paralytic poliomyelitis in the Russian Federation from 2017 to 2022, according to the State Reports of Rospotrebnadzor, is shown in

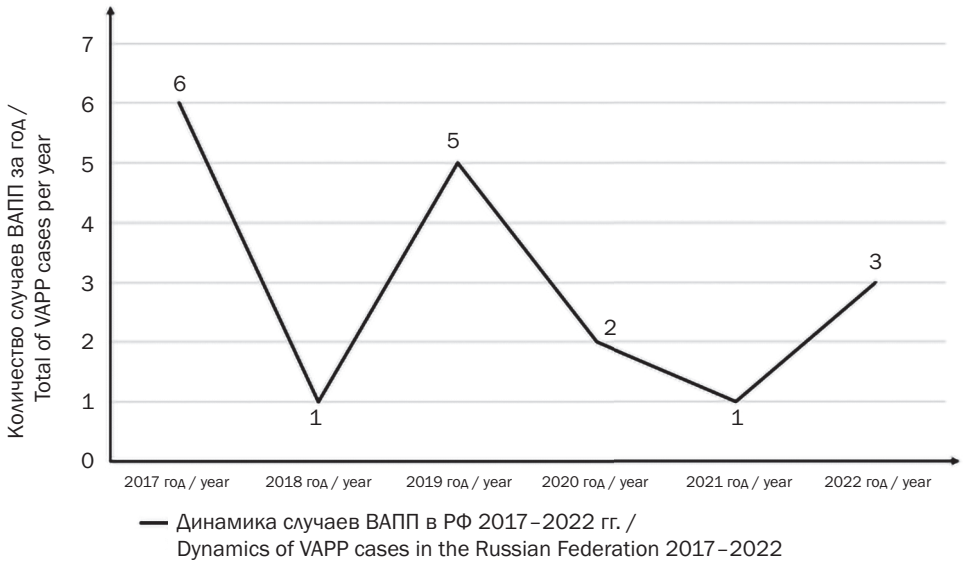

Fig. 4. Dynamics of vaccine-associated paralytic poliomyelitis (VAPP) cases in the Russian Federation (2017–2022 years)

Рис. 4. Динамика случаев вакцин-ассоциированного паралитического полиомиелита (ВАПП) в Российской Федерации (2017–2022 гг.)

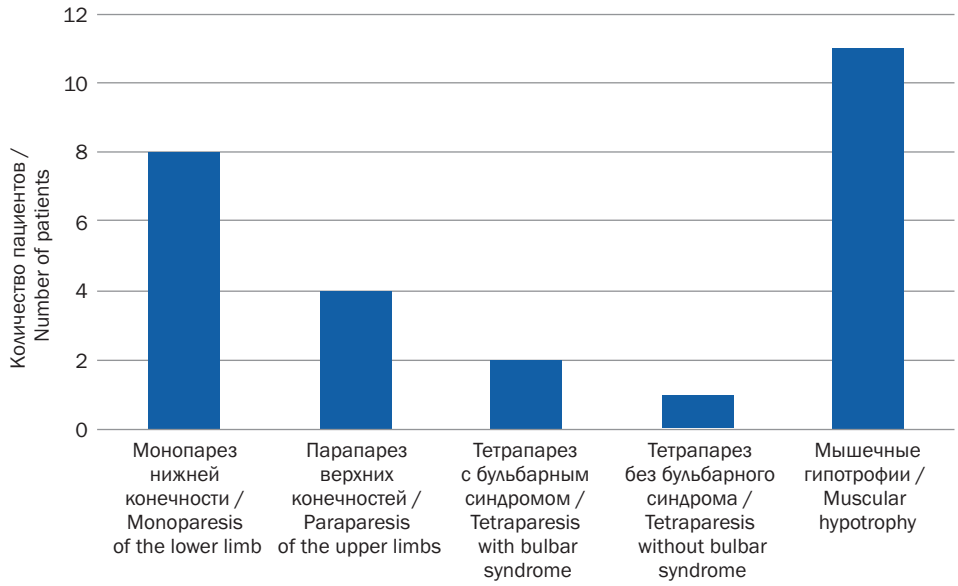

Fig. 5. Neurological manifestations of vaccine-associated paralytic poliomyelitis in oral polio vaccine recipients

Рис. 5. Неврологические проявления вакцин-ассоциированного паралитического полиомиелита у реципиентов оральной полиомиелитной вакцины

Figure 4. The largest number of detected cases was observed in 2017 and 2019 [26–30].

In the study by A.K. Shakaryan et al. (2019), an analysis of VAPP cases from 2006 to 2016 was conducted on individuals who received OPV as part of the vaccination – recipients of OPV and individuals in contact with the recipients of OPV who developed vaccine-associated paralytic poliomyelitis. Muscle hypotrophy, para- and monoparesis of the lower limbs predominated in persons in contact with recipients. In recipients of OPV muscle hypotrophy, para- and monoparesis of the lower limbs predominated, and tetraparesis with bulbar palsy was also encountered, which was not found in persons in contacts with recipients of OPV (Fig. 5, 6) [31].

In 2023, 1 case of VAPP was registered. Vaccine-derived polioviruses type 2 were isolated in two regions

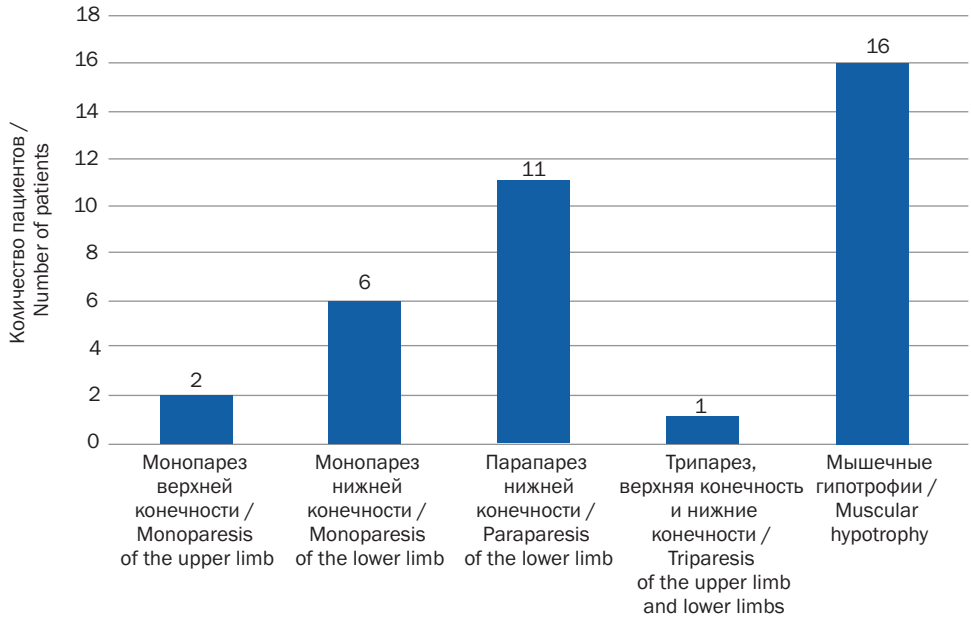

Fig. 6. Neurological manifestations of vaccine-associated paralytic poliomyelitis in contact persons

Рис. 6. Неврологические проявления вакцин-ассоциированного паралитического полиомиелита у контактных лиц

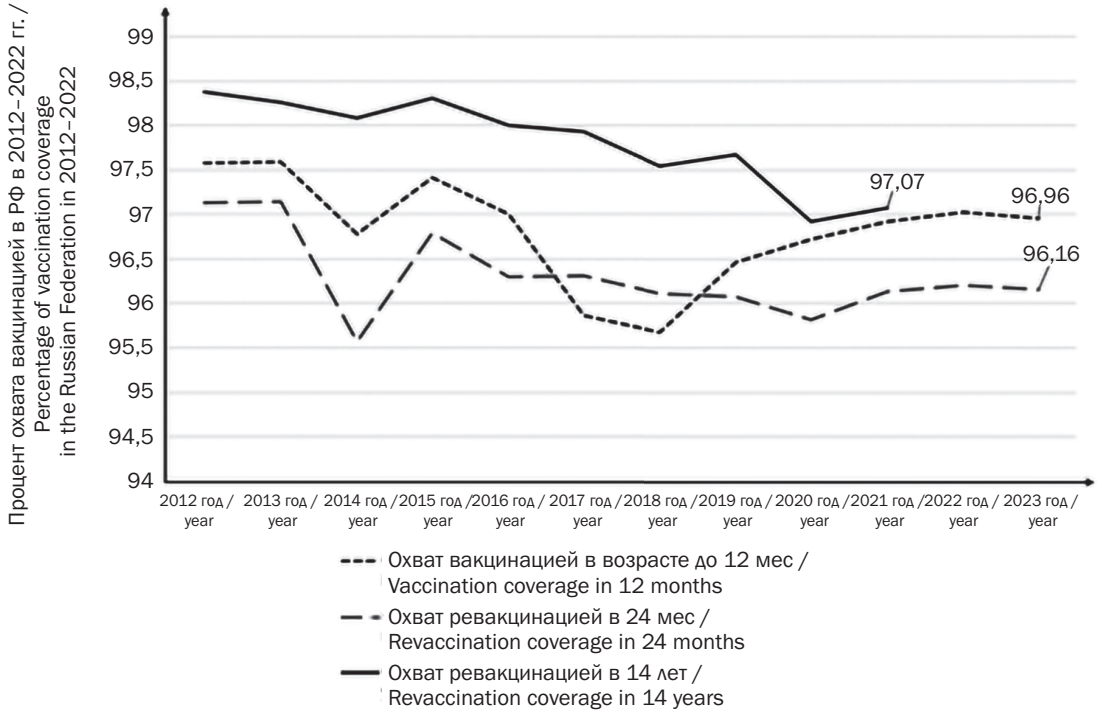

Fig. 7. Dynamics of polio vaccination coverage in the Russian Federation (2012–2023 years)

Рис. 7. Динамика показателей охвата вакцинацией против полиомиелита в Российской Федерации (2012–2023 гг.)

of the country. According to genome sequencing, the viruses are not related to each other and could have been isolated by individuals with immunodeficiency disorders. Rospotrebnadzor conducted an epidemiological investigation into this incident, organized a set of anti-epidemic and preventive measures, including immunization of the child population, in accordance with sanitary legislation and taking into account the WHO recommendations. As a result of the measures taken, the situation was localized, no new cases of isolation

of vaccine-derived poliovirus were recorded. The global situation and isolated findings of epidemiologically significant polioviruses, including as a result of importation, emphasize the relevance of the risks for the Russian Federation [5].

The dynamics of polio vaccination coverage rates in the RF in 2012–2023 are shown in Figure 7. Since 2022, according to the National Immunization Calendar of the Russian Federation, revaccination of children at 14 years of age has been replaced by revaccination at 6 years of age. Its rates were 88.1% in 2022 and 94.35% in 2023 [5].

Despite the high levels of vaccination coverage in the country as a whole, problems in the organization of immunoprophylaxis remain in a number of regions. In 2023, the coverage rate of children with timely immunization against polio at the age of 12 months was not achieved in 2 regions of the country (in 2022 — in 4), at the age of 24 months — in 4 (in 2022 — in 5), the coverage rate of the third revaccination at 6 years — in 20 (in 2022 — in 37) [5].

In 2023, in four federal subjects of the North Caucasus Federal District, catch-up supplementary immunization was held among all children aged 3 months to 9 years inclusive using inactivated and oral polio vaccines to increase the level of herd immunity to polioviruses. It was due to the isolation of vaccine-derived poliovirus type 1 in 2022 During the supplementary immunization program, high rates of poliomyelitis vaccination coverage were achieved, and measures to prevent VAPP were implemented [5].

In connection with the population migration from border states, immunization against polio was organized for unvaccinated or children under 14 years who have no data on preventive vaccinations that arrived during the year from Ukraine, the Donetsk and Lugansk People's Republics, and the Zaporizhye and Kherson regions. A total of 14,260 people were vaccinated [25].

Over the past 10 years (2014–2023), studies of material from 3,218 cases of acute flaccid paralysis and more than 70,000 healthy children from risk groups were conducted as part of polio surveillance. This made it possible to identify VAPP cases, as well as mutated vaccine-derived polioviruses of three types, including the import of cVDPV type 2 from the Republic of Tajikistan in 2021. A study of more than 140,000 wastewater samples showed the absence of circulation of WPV and cVDPV among the population of the Russian Federation [5].

CONCLUSION

Despite the activities carried out by the WHO, regions of Afghanistan and Pakistan currently remain endemic for wild poliovirus type 1. There are risks of the spread of WPV type 1 beyond the endemic regions due to military conflicts, unjustified refusals to vaccinate, non-compliance with vaccination schedules, the preservation of a non-immune layer of the population group in these countries and the incomplete scope of measures taken to fight against polio.

The prevalence of polio caused by cVDPV type 2 is much wider: it covers Africa and endemic countries. This is due to both the properties of the vaccine strains of polioviruses and the emergence of a non-immune layer of the population group in these regions along with the use of a live bivalent oral polio vaccine containing only poliovirus types 1 and 3. The new monovalent oral polio vaccine has reduced the incidence of poliomyelitis caused by cVDPV type 2.

In the Russian Federation, there remains a risk of importation of both wild and circulating vaccine strains of polio from other countries due to population migration from countries with low polio vaccine coverage. In the RF, there are isolated VAPP-cases caused by non-compliance with sanitary standards for general immunization.

Thus, the problem of polio remains relevant not only in endemic wild poliovirus regions, regions with circulation of cVDPV type 2, but also in the Russian Federation.

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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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.

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THE EFFECT OF GENERAL ANESTHETICS ON COGNITIVE FUNCTIONS IN CHILDREN

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ABSTRACT. ***Introduction.*** Recent work and accumulated knowledge over several decades have shown that general anesthetics are potentially toxic to a child's developing brain. In many animal studies, it has been found that after exposure to anesthesia, neuroinflammation, apoptosis of neurons occurs at certain stages of brain development, and persistent cognitive impairment subsequently forms. A number of cohort studies are alarming in assessing the intellectual development of children who underwent general anesthesia at the age of 3 years. Several studies have found a link between the use of anesthesia in early childhood and the subsequent development of cognitive impairment, the appearance of learning problems. ***The purpose of the work*** is to present the results of a systematic review of publications on the problem of the effect of general anesthesia on the cognitive functions of a child. The search for publications was carried out by analyzing PubMed electronic bibliographic databases. ***Result.*** In our study the analysis of preclinical studies, as well as the largest retrospective and prospective clinical studies, is carried out; problems in identifying biomarkers associated with the neurotoxicity of general anesthetics are identified; the role of surgical intervention and changes in homeostasis in the formation of postoperative cognitive dysfunction is considered. ***Conclusion.*** At the moment, there is no convincing evidence that a single and short exposure (less than 1 hour) to general anesthesia in early childhood has a causal relationship with a negative effect on the neurocognitive functions of the child. Repeated exposure to anesthetics can lead to deterioration of some of the child's skills. There is a need to conduct new studies related to the prolonged effect of general anesthesia (more than 1 hour) on the nervous system of children, to identify the dependence of the severity of neurotoxicity on the duration of anesthesia and the choice of anesthetic. There is a need to identify suitable biomarkers associated with the neurotoxicity of general anesthetics. It is necessary to study the role of surgical intervention, the type of operation, and temporary changes in systemic homeostasis in the formation of postoperative cognitive dysfunction in children.

KEYWORDS: *general anesthesia, neurotoxicity, anesthetics, biomarkers, postoperative cognitive dysfunction, childhood*

ВЛИЯНИЕ ОБЩИХ АНЕСТЕТИКОВ НА КОГНИТИВНЫЕ ФУНКЦИИ У ДЕТЕЙ

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РЕЗЮМЕ. ***Введение.*** Последние работы и накопленные за несколько десятилетий знания показали, что общие анестетики потенциально токсичны для развивающегося мозга ребенка. Во многих исследованиях, проведенных на животных, было установлено, что после воздействия анестезии на определенных этапах развития головного мозга возникает нейровоспаление, апоптоз нейронов и впоследствии формируются стойкие когнитивные нарушения. Вызывает настороженность ряд когортных исследований при оценке интеллектуального развития детей, перенесших общую анестезию в возрасте до трех лет. В нескольких работах обнаружена связь между применением наркоза в раннем детском возрасте и последующим развитием нарушений когнитивных функций, а также появлением проблем в обучении. ***Цель работы*** — представить результаты систематического обзора публикаций о проблеме влияния общей анестезии на когнитивные функции ребенка. Поиск публикаций был осуществлен путем анализа электронных библиографических баз данных PubMed. ***Результаты.*** Произведен разбор доклинических исследований, а также наиболее крупных ретроспективных и проспективных клинических работ. Обозначены проблемы в выявлении биомаркеров, связанных с нейротоксичностью общих анестетиков. Рассмотрен вопрос роли хирургического вмешательства и изменения гомеостаза в формировании послеоперационной когнитивной дисфункции. ***Заключение.*** На данный момент нет убедительных данных о том, что однократное и короткое воздействия (менее 1 часа) общей анестезии в раннем детском возрасте имеет причинно-следственную связь с негативным влиянием на нейрокогнитивные функции ребенка. Многократное воздействие анестетиков может привести к ухудшению некоторых навыков ребенка. Имеется необходимость в проведении новых исследований, связанных с продолжительным воздействием общей анестезии (более одного часа) на нервную систему детей и зависимости выраженности нейротоксичности от длительности анестезии и выбора анестетика. Существует необходимость в определении подходящих биомаркеров, связанных с нейротоксичностью общих анестетиков. Требуется проведение новых работ, изучающих роль хирургического вмешательства, вида операции, временного изменения системного гомеостаза в формировании послеоперационной когнитивной дисфункции у детей.

КЛЮЧЕВЫЕ СЛОВА: *общая анестезия, нейротоксичность, анестетики, биомаркеры, послеоперационная когнитивная дисфункция, детский возраст*

INTRODUCTION

The anesthesiologist informs children and parents about the possible risks associated with the use of anesthesia. Some complications, such as damage to the lips and teeth, anaphylaxis, regurgitation of gastric contents into the airways, sore throat, nausea and vomiting, may occur immediately. But there is a risk that is much more difficult to assess — the effect of the anesthetic on the developing brain of the child. Parents are increasingly interested in the neurocognitive functions of their children after general anesthesia, although many anesthesiologists still rarely assess the possible risks of developing cognitive dysfunction during the preoperative check-up. The relevance of the topic is due to the prevalence of surgical interventions and diagnostic studies requiring anesthesia during periods of development of the child's nervous system. Initially, the results obtained during pre-clinical animal research showed that the basis for changes in cognitive functions after anesthesia is neuronal apoptosis (programmed death) during the formation of synaptic connections [1]. The observed neurodegeneration caused alarm, and many animal research, as well as clinical trials, began to focus on this issue.

The article provides a systematic review of publications on the problem of the effect of general anesthesia on cognitive functions in children. The initial data of preclinical research, early retrospective clinical analyses on this topic, and the results of recent cohort studies are discussed. Based on this, the problems and prospects for new studies are identified. The review includes articles published from 1981 to 2023. The search for publications was carried out by analyzing PubMed electronic bibliographic databases in the spring of 2024. The research request included the following words and phrases: post-operative cognitive dysfunction, anesthesia. Based on the search results, 960 records were identified in the databases, of which 783 articles were recognized as potentially relevant. When assessing the relevance of the content of these articles, a set of 45 publications was formed, presented below. The analysis was carried out on articles published in English and Russian.

ANIMAL RESEARCH

The study of the effect of anesthetics on the central nervous system is an important aspect of the safety of using these agents in clinical practice. Studies of the toxic effect of general anesthetics on the developing brain have been conducted for several decades and continue to be actively carried out until now. As early as 1981, an article entitled “Exposure to halothane and enflurane affects learning function of murine progeny” was published in the journal Anesthesia & Analgesia [2]. This experiment showed that mice exposed to halothane or enflurane in utero were worse in maze performance than control group, which was not exposed to anesthetics. Moreover, in some cases, learning disorders were also detected in the next generation of mice exposed to halothane.

Important study was published in 1999 in the journal Science, “Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain” [1]. This work established a link between early exposure to NMDA receptor antagonists and the development of neuroapoptosis in rat pups. In the following years, the number of studies and publications only grew, and it became increasingly clear that the effects of anesthetics on the central nervous system of animals are indeed toxic. Exposure to anesthetics can cause both neuroapoptosis and significant behavioral disturbances in animal models, such as mice, rats, guinea pigs, and non-human primates [3–5].

The fact that in non-human primates adverse effects were detected a comprehensive manner at the biochemical, morphological, histopathological and behavioral levels was of particular concern [6]. The results in the presented studies raised a new question: can the data obtained in animal research be extrapolated to humans? Given the growing amount of information obtained from preclinical research, the United States Food and Drug Administration (FDA) has made recommendations in 2007 that *elective procedures involving general anesthesia in children under 3 years of age should be delayed whenever possible*. The committee also concluded that *additional studies are needed to understand the significance of data on the effects of anesthetics on animals for children who*

will be exposed to general anesthesia. Since then, many animal studies and clinical trials have focused on this issue [7].

At the same time, the FDA statement provided was the impetus for new studies that needed to assess neurological disorders in children exposed to general anesthesia in the long term. With the support of the FDA and IARS (International Association for Reconciliation Studies, International Anesthesia Research Society), the SmartTots program (https://smarttots.org/) is being created. Its aim is to assess the effect of anesthetics on children's development, as well as to assist and support scientists working in this field. It was after the FDA statement of 2007 that several large and important studies were conducted on this topic.

RISING ALARM

Several studies were published at once in 2009, addressing the topic of postoperative cognitive dysfunction in children. One of them is an observational study by C. DiMaggio et al. [8]. A cohort of 383 children who had undergone inguinal hernia repair within the first three years of life was selected. They were compared with 5,050 subjects of similar age who had not had surgery performed for up to three years. It was found that behavioral disorders and developmental delays were detected more than twice as often in children who had undergone surgery. Then the same authors conducted another large study to determine the influence of environmental factors [9]. A cohort of 10,450 siblings was formed, from which a group of 304 children exposed to general anesthesia before the age of three years was isolated. A comparison was also made with 10,146 siblings who did not undergo surgery and were not exposed to general anesthetics before the age of three years. The study found that behavioral deviations and neurodevelopmental disorders were 60% more common in children who had surgery. Moreover, the estimated odds ratio for developmental or behavioral disorders increased with multiple surgeries. It was 1.1 (95% CI 0.8–1.4) for one surgery, 2.9 (94% CI 2.5–3.1) for two surgeries, and 4.0 (95% CI 3.5–4.5) for three or more surgeries.

In 2009, the results of a population-based retrospective study by R.T. Wilder et al. were also published, which examined the effects of anesthetics on children under four years of age. Scientists selected a group of 5,357 children, of which 593 children were exposed to general anesthesia. The study found that subjects who had undergone general anesthesia once before the age of four showed results comparable to the control group. However, the results in reading, writing, and mathematics in children had been given general anesthesia several times were noticeably worse, and learning difficulties were detected more often [10].

One of the stages of research was the comparison of twins. M. Bartels et al. published an article in which 1143 pairs of identical twins from the Netherlands Twin Register were analyzed [11]. Separately, pairs of twins were identified in which one or both of the siblings had undergone general anesthesia before the age of three. It is worth noting that the authors did not take into account the duration of general anesthesia and the nature of the surgical intervention. The results showed that at age 12, the twins exposed to anesthesia before age 3 had significantly lower academic performance and more cognitive problems than the twins who were not exposed to anesthesia. It is interesting that study presented has an important nuance: the same poor academic performance was demonstrated by the twins who did not undergo anesthesia from the observed pairs, not differing directly from their exposed siblings. This information excludes a causal relationship between the effects of anesthetic on the child's nervous system.

It should also be mentioned that in addition to the general study, the above-mentioned work by C. DiMaggio et al. [9] also assessed 138 pairs of twins, in which one child had undergone surgery and the other had not. In this part of the analysis, it was found that, just as in the article by M. Bartels et al., when assessing pairs of discordant twins, the risk of developing neurological disorders was not significantly associated with the effects of general anesthesia. Such discrepancies in the results raised even more questions, and it became clear that a more in-depth analysis of the existing problem was needed. There was a need to conduct larger-scale studies, including randomized

clinical trials [12]. Such studies included **GAS**, **MASK**, and **PANDA**, which will be discussed in more detail below.

GENERAL ANAESTHESIA OR AWAKE-REGIONAL ANAESTHESIA IN INFANCY (GAS)

The aim of the first multicenter randomized clinical trial was to identify the negative effects of a general anesthetic (sevoflurane) on the development of the nervous system of a child who underwent anesthesia in infancy. The study included 722 children from 7 countries at a postconceptional age of up to 60 weeks, born no earlier than 26 weeks' gestational age. All observed patients underwent inguinal hernia repair. The children were divided into two equal groups. In the first group, regional anesthesia was performed subjects in a waking state using bupivacaine or levobupivacaine. In the second group, sevoflurane was used for induction and maintenance of anesthesia. No additional opioid or nitrous oxide administration was permitted, but regional blockades with bupivacaine were allowed to provide postoperative analgesia. It is noteworthy that the mean duration of anesthesia in the general anesthesia group was 54 minutes. Follow-up neurodevelopmental assessments were performed at age 2 years (adjusted for prematurity) and for 4 months after age 5. In total, the study was completed for 205 subjects using awake-regional anesthesia and 242 using general anesthesia.

Based on the results of tests on the mental and neurocognitive development of children at the age of two and five years, no convincing differences in the intellectual development of the two groups were found. The results of the presented work allowed the authors to conclude that the effect of general anesthetic on a child in early infancy will not cause significant neurocognitive or behavioral disorders at the age of two and five years [13, 14].

MAYO ANESTHESIA SAFETY IN KIDS (MASK)

In the observational study under review, the authors aimed to evaluate the effect of general anesthetics on the nervous system of children who had undergone anesthesia several times before the age of three. The researchers selected a group of children born from January 1, 1994 to December 31, 2007. During the medical record review, the subjects were divided into three groups: 411 children who had not undergone anesthesia, 380 children who had undergone anesthesia once, and 206 children who had undergone anesthesia multiple times. Each group was subdivided into two age categories: from 8 to 12 years (preadolescence) and from 15 to 19 years (adolescence). It is noteworthy that such distribution was aimed not only at separating by age characteristics, but also due to the wider introduction of sevoflurane into anesthetic practice for the preadolescent group. Mean duration of general anesthesia was 45 and 187 minutes for patients who underwent general anesthesia once and multiple times, respectively. At the same time, 2/3 of the subjects who underwent multiple exposures were under anesthesia for more than two hours. According to the study, the most frequently used anesthetics were sevoflurane and nitrous oxide, and the most common types of surgical interventions were ENT and cardiovascular surgeries. Each child was assessed for intellectual development using the WASI (Wechsler Abbreviated Scale of Intelligence), then attention, reaction, visual-motor memory, etc. were analyzed using various tests. In addition, the parents of the children participating in the study compiled reports on the behavior, learning, and development of their child.

The results showed that subjects who had been repeatedly exposed to general anesthesia performed only slightly worse on the intelligence test than the group who had been exposed once and the children who had not been anesthetized at all. The available data allowed the authors to conclude that exposure to general anesthetics before the age of three is not associated with reduced intelligence in preadolescence and adolescence. Regarding the results of the child's skills, it is worth noting that only children exposed to repeated general anesthetics showed a decline in information processing speed and fine motor skills. Along with this, other skills among the groups, such as reaction, attention, verbal expression of thoughts, etc., were at a comparable level. It is also noted that parents of those children who had been repeatedly anesthetized more often reported

problems related to their children's behavior and reading [15].

PEDIATRIC ANESTHESIA NEURODEVELOPMENT ASSESSMENT (PANDA)

The PANDA project is a large multicenter study that aims to evaluate the development of the nervous system in children who underwent a single exposure to general anaesthesia for inguinal hernia repair before the age of three years. Two groups were examined: the children who had undergone anesthesia, and subjects' brothers and sisters who had not been exposed to anesthesia. Siblings had to be close in age with a difference of no more than three years. Children aged 8 to 15 years were assessed for cognitive function, as well as intelligence and behavior. A total of 105 pairs of siblings were analyzed in the study. All the patients who underwent anesthesia received inhalational anesthetics (43 sevoflurane, 5 isoflurane, 57 sevoflurane and isoflurane). Both inhalational and intravenous anesthetics (propofol, thiopental, ketamine and midazolam) were given to 28 patients. Additional opioid analgesia was administered to 75 subjects and 39 children received additional spinal anesthesia. Mean duration of general anesthesia was 84 minutes. The study found no significant differences in intelligence, memory, attention, behavior, or information processing speed among children who underwent general anesthesia before age three compared with their siblings who were not undergoing general anesthesia [16].

The results of the above-mentioned **MASK**, **GAS** and **PANDA** studies in many review articles are often considered together and cause heated discussions [17–20]. Subsequently, these works became the foundation for new studies on the effect of anesthesia on the nervous system of the child.

UNRESOLVED ISSUES AND NEW RESEARCH

The above studies were unable to fully resolve the issues raised by the FDA in 2007, which focused on the risks of general anesthesia in children. However, analyzing the results obtained in these studies, we can form a number of preliminary conclusions:

- probably, short-term single exposure to general anesthesia does not affect the neurocognitive functions of children in subsequent development;
- it is worth assuming that repeated exposure to general anesthetics has harmful effects on a number of children's skills, which causes reasonable alertness;
- there remains uncertainty associated with the long-term effect of general anesthesia (more than 1 hour) on the nervous system of children and dependence of the severity of neurotoxicity on the duration of anesthesia.

Despite many unanswered questions, in 2016 the FDA issued a new, tougher statement: "*Repeated or lengthy use of general anesthetics and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Healthcare professionals should balance the benefits of anesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years*" [21]. This notice caused a lot of discussion and debate among anesthesiologists [22–24]. The European Society of Anaesthesiology and Intensive Care even issued a response that they do not share the opinion of the FDA specialists. This was argued by the fact that at the moment there is no convincing data, confirmed by human studies, that would indicate any effect of prolonged or continuous anesthesia on neurocognitive abilities and development of children [25].

Debate continues to this day, but one thing remains clear: there are still insufficient studies to draw clear final conclusions [26–28]. Due to the difficulty of conducting randomized clinical trials of the neurotoxic effect of anesthetics and their impact on children's cognitive skills, only one large project, GAS, has been implemented. According to the analysis of published articles, since 2018, due to the shifting focus towards problems associated with the COVID-19 pandemic, interest in research on the neurotoxic effect of anesthetics has somewhat decreased [29]. However, scientific interest in the problem is gradually reviving, and a number of large clinical trials are currently underway. The study of Professor P. Szmuk et al. on the

T-REX trial stands out. A multicenter randomized clinical trial is being conducted, which compares infants who have been administered standard dose of sevoflurane with children who underwent combined anesthesia with low doses of sevoflurane, dexmedetomidine and remifentanil [30]. Duration of anesthesia considered in the study is 2 hours and more. A total of 440 newborns requiring surgery are randomly assigned to receive different types of anesthesia: standard doses of sevoflurane or combined anesthesia. The results of this research should clarify the impact of prolonged general anesthesia on the developing child's brain.

BIOMARKERS AND NEUROIMAGING

The study of neurotoxicity of general anesthetics is complicated by the difficulty of assessing cognitive status in young children. Most studies evaluate children's cognitive functions primary school or school age. Given the assumption that young patients under three years are most susceptible to the effects of anesthetics [21], there is a long delay between exposure to general anesthesia and assessment of its effects [31]. There is a need for long-term observation of children who have undergone anesthesia at an early age, and the likelihood of distortion of results due to environmental and other factors increases. Identification of suitable biomarkers associated with general anesthetic neurotoxicity may be extremely valuable for clinical trials. Biomarker detection could help assess interim outcomes and understand the mechanism of central nervous system injury. And if biomarker values can be linked to long-term outcomes, it may be possible to detect injury at an earlier stage, thereby reducing the time between anesthetic exposure and assessment of the effect. This, in turn, would reduce the need for long-term follow-up in clinical trials.

One of the biomarkers proposed for consideration by a number of authors is the level of **S100β** protein in serum or cerebrospinal fluid. Animal research has shown that S100β is effective in detecting acute neurological injury to the developing brain caused by general anesthesia [32–34]. An analysis of several studies has revealed a correlation between postoperative cognitive dysfunction and elevated S100β levels in adult patients [35]. However, studies conducted in children have had mixed results [36–38], and the assessment of the relationship between changes in S100β levels and postoperative cognitive dysfunction in children requires further study. In addition, obtaining cerebrospinal fluid from conscious children also causes certain difficulties, which complicates the use of cerebrospinal fluid biomarkers in clinical trials.

In connection with these facts, neuroimaging has become another alternative assessment of the neurotoxicity of anesthetics [39]. In 2015, a study was published in which magnetic resonance imaging (MRI) data showed a decrease in gray matter volume of in the brain of children who underwent anesthesia before the age of four [40]. Also, a recent study assessed the results of the MRI and neuropsychological indicators in 102 children aged 9 to 10 years, 24 of whom were exposed to general anesthesia in infancy. It turned out that subjects who were exposed to anesthesia had a decrease in gray matter volume of the right inferior frontal gyrus, as well as reduction in the ability to control their emotions [41]. In addition to measuring the volume of gray matter and other structures, MRI in children can be used to assess the interaction between different areas of the central nervous system (CNS) both during brain activation during certain cognitive tasks and tests and at rest without performing any tasks [42, 43]. It should be emphasized that there are currently no data that have clearly established the relationship between changes in the CNS according to MRI results and the presence of postoperative cognitive dysfunction in children, and future studies should be aimed at assessing structural disorders in combination with neuropsychological analysis. It should be noted that, although this method is promising, it has an obvious disadvantage — the difficulty of use in young children who require sedation for MRI.

IMPACT OF SURGICAL INTERVENTION AND OTHER FACTORS

Many studies have focused on the effects of general anesthetic on children's cognitive function. However, there is still little specific information on the role of surgery and type of surgical procedure on postoperative cognitive dysfunction in children. There is a lack of understanding of how a particular type of sur-

gery, combined with different types of general anesthesia, may affect a child's developing brain. For example, a study on seven-day-old rats found that prolonged anesthesia after exposure to nociceptive stimuli resulted in significantly greater apoptosis in the central nervous system compared to the situation when only general anesthesia was used [44]. An isolated study of the effect of surgical intervention on cognitive functions in humans has a number of difficulties, primarily ethical ones, because the creation of a group to perform an operation in children without any anesthesia is impossible. It is necessary to analyze non-surgical diagnostic and therapeutic procedures that require anesthesia in comparison with surgical interventions in future studies.

Another important issue is the impact of temporary changes in systemic homeostasis during general anesthesia on the developing brain of the child. There is evidence that changes in homeostasis, such as hypoxia/hyperoxia, hypoglycemia/hyperglycemia, changes in electrolyte composition, and low blood pressure, lead to worsening of postoperative neurological outcomes in children [27, 45]. But, there is still little information on how neurological disorders due to changes in homeostasis are related to the patient's age, duration, type of anesthesia and surgery. There are currently no studies identifying causal relationship. It is clear that new studies to investigate the impact of changes in systemic homeostasis during and after surgery on the development of the nervous system are needed.

CONCLUSION

A large amount of evidence on the neurotoxicity of anesthetics was collected animal research and clinical trials in children. However, there is currently limited information received on neurocognitive risk after of exposure to general anesthesia. The GAS, MASK, and PANDA studies have provided some preliminary conclusions that can be used in anesthesiology practice to assess the risk of postoperative cognitive dysfunction. The results of the studies showed that single and short exposure (less than 1 hour) to general anesthesia does not affect children's neurocognitive function. But, repeated exposures to anesthetics may impair some of a child's skills. Future additional studies are needed to better understand the conditions that may lead to risk. The effects of different drugs and drug combinations, impact of anesthetic dose and frequency of repeated anesthesia should be studied.

In addition, many other issues remain unsolved. There is still uncertainty regarding the effects of general anesthesia for more than one hour on the nervous system of children. The study of Professor P. Szmuk et al. on the T-REX trial should clarify this question. There is a need to identify more precise biomarkers associated with general anesthetic neurotoxicity for the assessment of intermediate outcomes. This, in turn, may resolve one of the major problems in conducting prospective studies in this field. Biomarker detection should be a promising topic for new studies in the future. It is also important to develop methods to identify anatomical damage after general anesthesia and establish a putative association with adverse neurocognitive outcomes in children. MRI seems to be one of the possible methods for detecting damage. In addition to the effect of anesthesia, new studies should also determine the role of surgery, type of surgical procedure and temporary changes in systemic homeostasis in the development of postoperative cognitive dysfunction in children.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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THE ROLE OF DIET IN THE DEVELOPMENT AND TREATMENT OF RHEUMATIC DISEASES IN CHILDREN

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ABSTRACT. There is a fairly large number of publications in the modern Russian scientific literature on the role of diet in the development and course of both rheumatic diseases in adults and various chronic diseases in children. At the same time, the issues of diet therapy of rheumatic diseases in children are practically not discussed in modern Russian-language scientific publications. The only Russian-language scientific article devoted to the diet therapy of juvenile arthritis was published more than 20 years ago. The review of foreign publications on the role of diet in the development and treatment of various rheumatic diseases in children, namely juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile dermatomyositis, IgA vasculitis, Kawasaki disease and familial Mediterranean fever, is presented. Most of the studies were conducted with patients suffering from juvenile idiopathic arthritis and concerned the role of gluten-free, low-calorie ketogenic, specific carbohydrate diets, intestinal microbiota and enteral nutrition in its treatment, assessment of nutritional status in juvenile idiopathic arthritis, the influence of parental eating behavior, maternal nutrition during pregnancy and nutrition of the child in the first year of life on risks of developing juvenile idiopathic arthritis.

KEYWORDS: *diet therapy, rheumatic diseases, children*

РОЛЬ ДИЕТЫ В РАЗВИТИИ И ЛЕЧЕНИИ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

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РЕЗЮМЕ. В современной отечественной научной литературе имеется достаточно большое количество публикаций, посвященных роли диеты в развитии и течении как ревматических заболеваний у взрослых, так и различных хронических заболеваний у детей. При этом вопросы диетотерапии ревматических заболеваний у детей в современных русскоязычных научных публикациях практически не обсуждаются. Единственная русскоязычная научная статья, посвященная диетотерапии ювенильных артритов, была опубликована более 20 лет назад. В настоящей статье представлен обзор зарубежных публикаций, посвященных роли диеты в развитии и лечении различных ревматических заболеваний у детей, а именно ювенильного идиопатического артрита, ювенильной системной красной волчанки, ювенильного дерматомиозита, IgA-васкулита, болезни Кавасаки и семейной средиземноморской лихорадки. Большинство исследований было проведено с участием пациентов, страдающих ювенильным идиопатическим артритом, и касались роли безглютеновой, низкокалорийной кетогенной, специфической углеводной диеты, кишечной микробиоты и энтерального питания в его лечении, оценки нутритивного статуса при ювенильном идиопатическом артрите, влияния пищевого поведения родителей, питания матери во время беременности и питания ребенка на первом году жизни на риски развития ювенильного идиопатического артрита.

КЛЮЧЕВЫЕ СЛОВА: *диетотерапия, ревматические заболевания, дети*

INTRODUCTION

The etiology of the vast majority of rheumatic diseases remains unknown, and drug therapy does not always provide stable remission. New possible theories of the origin of autoimmune rheumatic diseases and various methods of alternative and complementary medicine in their treatment continue to be studied. The Russian scientific literature contains a large number of publications on the role of diet in adult patients with gout and rheumatoid arthritis [1–4]. A large number of Russian-language scientific articles are also devoted to diet therapy of various chronic diseases in children, most of which concern gastrointestinal diseases [5, 6]. However, there are also a sufficient number of modern publications devoted to the effectiveness of a gluten-free diet of autism spectrum disorders [7], efficiency of a ketogenic diet of epilepsy [8], and nutritional features of cerebral palsy and other neurological disorders [9]. Issues of diet for rheumatic diseases in children have been practically not discussed in Russian publications in recent years. The only Russian-language scientific article devoted to diet therapy of juvenile arthritis was published more than 20 years ago [10]. More modern publications on this topic, as well as studies devoted to the role of diet in the development and treatment of other rheumatic diseases in children, were not found in the available Russian-language literature.

AIM

The aim of the study is to review foreign publications on the role of diet in the development and treatment of rheumatic diseases in children.

MATERIALS AND METHODS

A search was performed in the PubMed database for articles published for all time up to April 28, 2024.

On request of "diet, juvenile idiopathic arthritis" were found 94 articles in total. Of these, 34 articles did not address the effects of diet on the development and course of juvenile idiopathic arthritis (JIA), and 23 articles were devoted to other diseases. Also, the full text of 10 articles from 1964–1989 was unavailable, the results of 8 studies from 1990–2000 were presented in a Russian-language review published in 2003 [10] and were not analyzed separately within the framework of this review, and 19 articles from 2003–2024 were included in the review [11–29].

On request of "diet, juvenile systemic lupus erythematosus" 13 articles were found, 5 of them did not concern the influence of diet on the development and course of juvenile systemic lupus erythematosus (JSLE), 3 articles were devoted to other diseases, 5 articles from 2009–2021 were included in the review [20, 27, 30–32]. Among them, 2 articles concerned not only JSLE, but also JIA, and were found using the previous request [20, 27].

On request "diet, juvenile dermatomyositis" 19 articles were found, 5 of them did not address the effects of diet on the development and course of juvenile dermatomyositis (JDM), 8 articles were devoted to other diseases. Full text of 4 articles from 1967–1984 was unavailable, 2 articles from 2016 and 2020 were included in the review [27, 33]. Among them, one article was devoted to JDM, JIA and JSLE and, accordingly, was also found using two previous requests [27].

On request "diet, child, vasculitis" 48 articles were found, of which 11 articles were on systemic vasculitis in children, but did not address the effects of diet on their development and course, 23 articles were devoted to other diseases or systemic vasculitis in adult patients. Among them, one publication was devoted to the clinical observation of a positive response to gluten-free diet in uveitis in a nine-year-old girl with celiac disease and type 1 diabetes mellitus. Full text of 8 articles from 1969–1984 was unavailable, 4 articles devoted to IgA vasculitis, 2019–2021 [34–37], 2 articles devoted to Kawasaki disease, 2013–2016 were included in the review [38, 39].

On request "diet, child, familial Mediterranean fever" 13 articles were found, 8 articles did not concern the influence of diet on the development and course of familial Mediterranean fever (FMF). Full text of 3 articles from 1964–1995 was unavailable, 2 articles from 2020 and 2021 were included in the review [40–41].

The summary results of the search, inclusion, and exclusion of articles are shown in Figure 1.

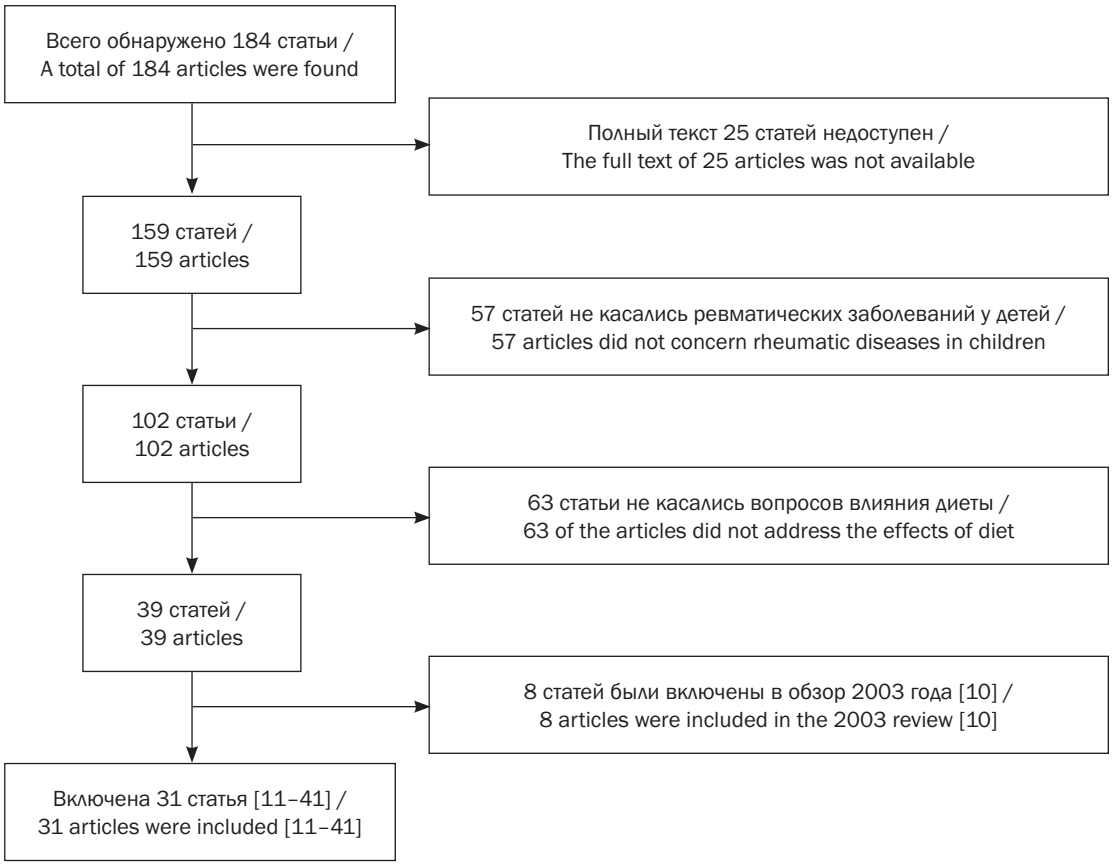

Fig. 1. Summary results of the conducted search, inclusion and exclusion of articles

Рис. 1. Суммарные результаты проведенного поиска, включения и исключения статей

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis is a heterogeneous group of chronic arthritis with onset before age 16 years, sometimes associated with extra-articular symptoms such as failure to thrive and gastrointestinal manifestations.

E.M. Little et al. in a 2019 study assessed the prevalence of the use of specific diets for JIA and the opinion of patients' parents about their effectiveness. An online survey was conducted for a year, in which about 20,000 people took part. Responses were received from 261 parents of patients with JIA. One third of patients (n=79) had experience with one or more specific diets, including gluten-free (66%), anti-inflammatory (41%), lactose-free (25%), vegetarian/vegan (20%). Of 79 parents of patients using the three most common diets, 50% reported reduced joint pain or swelling with the anti-inflammatory diet, 52% with gluten-free diet, and 65% with the lactose-free diet. However, the authors emphasize that prospective controlled studies are needed to test the effectiveness of a dietary approach to the treatment of JIA [11].

However, according to the 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis, there is little evidence to support the use of any specific restrictive diet in the treatment of JIA. Unnecessary use of restrictive diets such as gluten-free and lactose-free diets may worsen nutritional status and increase the risk of other negative effects such as treatment delays, unnecessary costs and inconvenience. A healthy, balanced, age-appropriate diet is essential for maintaining health and quality of life in patients with JIA [12]. However, the use of an appropriate diet is certainly indicated in the presence of comorbid JIA with celiac disease or lactase deficiency.

Comorbidity of juvenile idiopathic arthritis with celiac disease and possible role of gluten-free diet in its treatment

S.M. Al-Mayouf et al. in a 2003 study investigated the prevalence of celiac disease in JIA and the correlation between serological markers and histological diagnosis of celiac disease. Serological markers of celiac disease (anti-gliadin IgA and IgG antibodies, anti-reticulin antibodies, and anti-endomysial antibodies) were tested in 42 patients (18 boys, 24 girls, aged 5 to 15 years). Endoscopic intestinal biopsy was performed in patients with positive serological markers of celiac disease. The diagnosis of celiac disease was based on classical detection of villous atrophy and crypt hypertrophy. In 18 patients (42.8%) suffering from various types of JIA (10 of them were diagnosed with systemic JIA, 5 with polyarticular and 3 with oligoarticular), various serological markers of celiac disease were identified, and in most patients, an increase in the level of several antibodies was detected. Anti-gliadin IgG antibodies were high in 14 patients (77.8%), 4 patients (22.2%) had high levels of anti-gliadin IgA antibodies, 7 patients (38.9%) had anti-endomysial antibodies, and 1 patient (5.5%) had anti-reticulin antibodies. Sixteen patients underwent intestinal biopsy, and only one patient with anti-endomysial antibodies (2.4%) had typical features of celiac disease on biopsy. After switching to a gluten-free diet, the patient with celiac disease showed improvement in both growth parameters and joint symptoms [13].

P. Sadeghi et al. in a 2021 study assessed the prevalence of celiac disease in 78 patients with JIA (mean age 7.9±3.9 years) who did not respond sufficiently to its standard treatment. In 3 patients (3.8%) with the oligoarticular JIA, the level of IgA antibodies to tissue transglutaminase was higher than normal. None of them had clinical symptoms of celiac disease. There were no significant statistical differences between the groups of seropositive and seronegative for antibodies to tissue transglutaminase patients with JIA in terms of growth disorders, gender distribution and different types of JIA. In one patient, a 10-year-old boy with a diagnosis of oligoarticular JIA with knee joint involvement established more than 2 years before inclusion in the study, celiac disease was confirmed by histological examination. He was recommended a gluten-free diet, after 2 months of which all clinical manifestations of musculoskeletal system completely disappeared. The dose of antirheumatic drugs was gradually reduced and then completely discontinued, and during 12 months of observation, the patient did not have relapses of arthritis against the background of adherence to a gluten-free diet [14].

Low-calorie ketogenic diet in juvenile idiopathic arthritis

The low-calorie ketogenic diet has been used for over a century to treat refractory epilepsy. It is currently gaining popularity as a potential therapy for obesity, as well as various chronic inflammatory diseases, including rheumatic diseases, since ketone bodies may have an anti-inflammatory effect. However, there have been no studies on the ketogenic diet in children with JIA to date. M. Rondanelli et al. in 2023 published a clinical follow-up of a 22-year-old woman with class I obesity and JIA, diagnosed at the age of 4 years. The patient followed a low-calorie ketogenic diet combined with a specially recommended physical activity program for 4 months, which resulted in a decrease in body weight from 78.3 to 72.8 kg, a decrease in body mass index (BMI) from 30.8 to 28.6 kg/m2. Her waist circumference reduces from 80 to 73 cm, body fat mass from 28.1 to 23.2 kg, free body fat mass from 45.7 to 41.9 kg, and visceral adipose tissue from 3.5 to 2.9 kg. In addition, the patient experienced a decrease in joint pain and an improvement in laboratory parameters of inflammation (reduction of C-reactive protein (CRP) level from 17 to 5 mg/L and in erythrocyte sedimentation rate (ESR) from 95 to 31 mm/h was observed) [15].

Specific carbohydrate diet in juvenile idiopathic arthritis

The specific carbohydrate diet is a nutritionally balanced diet that eliminates many complex

carbohydrates, such as grains, dairy products except for fermented milk products, starchy vegetables, and sugars except for monosaccharides found in honey. In addition, most processed foods are excluded, as they may contain emulsifiers and additives that have a negative effect on the intestinal mucosa. Thus, the diet includes meat, poultry, fish, eggs, nuts, fruits, beans, peas, honey, fermented milk products, and hard cheeses. Grains, rice, corn, potatoes, dairy products with a high lactose content, refined sugar and sweets are excluded on this diet. In 2021, L. Berntson published the results of a pilot study of possible anti-inflammatory effects of the specific carbohydrate diet in children with JIA, which had previously shown a good anti-inflammatory effect in children with inflammatory bowel diseases. The study included 22 patients with various types of JIA (age 6.3–17.3 years), with low to moderate disease activity, who had 2 or fewer inflamed joints and an ESR less than 30 mm/h. These patients had changes in concomitant therapy for at least 12 weeks before and during study inclusion. A study was conducted on 15 children who followed the diet for 4 weeks (of the remaining 7 patients, 6 withdrew from the study prematurely due to low motivation, in 4 cases on the part of the patients themselves, in 2 cases on the part of their parents, one family withdrew from the study due to an acute psychosocial situation). In the 15 patients who completed the study, the diet significantly reduced morning stiffness ($p=0.003$) and pain ($p=0.048$). Physical function, assessed by the Children's Health Questionnaire, also improved ($p=0.022$). Of the 15 patients who completed the study, 7 had active arthritis at enrollment, which was not detected in 5 of the 7 patients after 4 weeks of diet. However, in all 7 children with active arthritis at enrollment, multiplex analysis showed significant reductions in 9 inflammatory proteins, including tumor necrosis factor alpha ($p=0.028$), after 4 weeks of diet. Based on these results, the authors concluded that the specific carbohydrate diet may have a significant positive effect on the course of JIA, but further research is needed [16].

In 2023, Hagström et al. [17] conducted semi-structured interviews with 12 children and 15 parents (12 mothers and 3 fathers) from 13 families who had participated in the 2021 pilot study of the specific carbohydrate diet by Berntson [16]. Majority of those surveyed found participation in the study useful, with 12 of the 13 families reporting positive effects such as reduced joint pain and morning stiffness. Many participants reported that they would be willing to participate in a similar study again. It was not easy for children to deal with the social-emotional consequences of following the diet. Their parents faced practical problems because dieting required hard work, time, and money. Fields identified as requiring additional support included finding simple, quick and child-friendly solutions, strengthening organizational skills in nutrition such as meal planning and preparing for an intervention, relating to social and emotional aspects [17].

The role of gut microbiota and enteral nutrition in juvenile idiopathic arthritis

In recent years, the field of studying the role of microbiota in the pathogenesis of various chronic rheumatic diseases has been actively developing. M. Arvonen et al. published a literature review on the role of microbiota in JIA in 2020. In the section on diet therapy for JIA, the authors noted that patients often ask whether there is a place for a dietary approach in the treatment of JIA. The most honest answer that doctors can give is that there is probably a place for diet therapy in JIA, we just don't know what exactly it should consist of. The authors emphasize that at the time of writing the review, the only dietary approach for JIA for which there are published data is enteral nutrition based on mixtures containing everything necessary for adequate nutrition, with the complete exclusion of conventional foods from the diet. The authors cite data published by L. Berntson in 2014 and 2016, as well as those reported by him in personal communication. According to these data, a positive experience with enteral nutrition was initially recorded in one patient with

a polyarticular variant of JIA, refractory to treatment with methotrexate and several tumor necrosis factor alpha inhibitors. Then the patient was treated with two courses of enteral nutrition, both of which led to an improvement in functional indicators, the number of inflamed joints and morning stiffness. This was followed by a pilot study of enteral nutrition in 13 children with active JIA. Six of them refused therapeutic nutrition within 1–2 weeks, which indicates poor tolerance of this approach. Among the remaining 7, all who completed a 3–8-week course of enteral nutrition experienced a reduction in the number of inflamed joints and morning stiffness [18].

L. Berntson et al. in a 2022 study investigated whether the anti-inflammatory effect of two dietary approaches for JIA (enteral nutrition and a specific carbohydrate diet), demonstrated by them earlier, is associated with changes in the gut microbiome. The study included 16 patients with JIA (age 7–17 years), 6 of whom were treated with enteral nutrition and 10 with a specific carbohydrate diet for 4-5 weeks. Their clinical and laboratory status was assessed before and after treatment. Reduction of disease activity was statistically significant in both dietary approaches (p=0.03 for each). Gut microbiome test showed an effect of both interventions on its overall composition, with the most striking result being a decrease in relative abundance of Faecalibacterium in enteral nutrition and bifidobacteria with the specific carbohydrate diet. Gut microbiome alpha diversity was statistically significantly reduced in the specific carbohydrate diet (p=0.04) but not with enteral nutrition (p=0.22). Although the study groups were small, it was clearly shown that both enteral nutrition and specific carbohydrate diet influence the gut microbiome in JIA [19].

Nutritional status assessment in juvenile idiopathic arthritis

M.C. Caetano et al. in a 2009 study assessed the diet of 48 children and adolescents with JIA (19 boys, 29 girls aged 3 to 19 years, mean age 12 years) and compared it with the clinical and anthropometric characteristics of the patients, as well as with the drugs used in their treatment. Malnutrition was found in 8.3% of patients with JIA, and obesity was present in 16.7%. In patients with JIA, excess energy intake was noted in 12.5%, excessive protein intake — in 75% and excessive lipid intake — in 31.3% of cases. Low iron intake was found in 29.2%, low zinc intake — in 87.5%, low vitamin A intake — in 87.5% and low vitamin B_6 intake — in 64.6% of patients with JIA. However, no significant association was found between intake of energy, macro- and micronutrients, disease activity and nutritional status. Qualitative analysis of the diet showed low consumption of milk and its derivatives, fruits and vegetables and excessive consumption of oils and fats, as well as sugar and sweets [20].

M.M. Grönlund et al. in a 2014 study assessed the effect of JIA, its subtypes and disease activity on anthropometric measurements, body composition, and nutritional parameters in 40 patients with JIA (19 boys, 21 girls aged 3–10 years) compared with 40 healthy children matched for age and gender. Significantly higher values for central and peripheral adiposity were found in JIA patients compared with in healthy controls (mean waist circumference 55.9±4.9 vs. 53.4±3.7 cm, p <0.0001, and biceps skinfold thickness 6.2±2.3 vs. 5.3±1.7 cm, p=0.035, respectively) and obesity/overweight was more common (30% vs. 12.5%, respectively, p=0.056). Energy intake (kcal/day) was significantly higher in patients with JIA (p=0.036). Nutritional biomarkers such as hemoglobin, albumin, cholesterol and its fractions, triglycerides, 25-OH-vitamin D and serum folate levels were comparable in both groups. JIA subtype and disease activity did not influence body composition, energy intake or nutritional biomarkers. Thus, even patients with JIA with low disease activity have been shown to have more pronounced central and peripheral adiposity and consume more energy than their healthy peers [21].

A. Hari et al. in a 2015 study evaluated the relationship between macronutrient intake, body composition (lean body mass and fat mass) and bone mineral content in 33 patients with JIA (18 boys, 15 girls, mean age 10.4±4.3 years, median disease duration 2 (1–4.5) years). The median of lean body mass was 19 (13.8–

33.1) kg, fat mass — 5 (3.4–9.1) kg, and bone mineral content — 1044.9 (630.4–1808.9) g. The authors found a positive correlation between lean body mass and dietary intake of carbohydrate (r=0.4; p=0.03). No significant association was found between lean body mass and lipid or protein intake. No association was found between fat mass, bone mineral content and intake of carbohydrates, lipids and proteins [22].

D. Gorczyca et al. in a 2017 study assessed the association between dietary intake of ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), their serum levels, and immune and inflammatory markers. The study involved 66 patients (16 boys, 50 girls aged 1.5 to 18 years, average age 8.6 years) with various types of JIA who were compared with a control group of 42 healthy children matched for age, gender, race, height, weight, and BMI. Dietary PUFA intake did not differ between the JIA and control groups. No relationship was found between intake of ω-3 and ω-6 PUFA and their serum levels. Total ω-6 PUFA and linoleic acid levels were higher in patients with inactive JIA than with active JIA. In patients with active and short-term disease (less than 3 months from diagnosis), arachidonic acid and docosahexaenoic acid levels were significantly lower than in the control group. Serum α-linolenic acid levels were significantly higher in patients with polyarticular JIA compared with patients with oligoarticular JIA and healthy peers. Negative relationship was established between serum ω-6 and ω-3 PUFA levels and the number of active joints, ESR, and CRP levels, and a positive relationship with the platelet count. The results of the study can identify a group of patients with JIA who may be recommended to take PUFAs in addition to their usual daily diet [23].

In late 2022 — early 2023, almost simultaneously, independently of each other, authors from Brazil [24], Greece [25] and the UK [26] published three reviews, including one systematic review and meta-analysis of studies on the relationship between nutritional status, dietary intake, symptoms and health-related quality of life in children and young people with JIA. It was shown that most of the studies indicate a suboptimal diet in children with JIA and the presence of a deficiency of a number of micronutrients that can be corrected with appropriate nutrition education conducted by experts. At the same time, some nutritional interventions, such as enteral nutrition and intake of ω-3 PUFAs may show some potential in terms of improving JIA symptoms. Thus, other dietary supplements, including vitamin D, as shown in a systematic review and meta-analysis by N. Zare et al. [26] are not associated with either improvement in JIA symptoms or improvement in the quality of life of patients.

The influence of parents' eating behavior

Parents' eating behavior, lifestyle, and food choices can directly affect their children's eating habits. L. Pereira et al. in a 2020 study assessed BMI, diet, physical activity, and lipid metabolite biomarkers in children and adolescents with various chronic rheumatic diseases, including the polyarticular JIA, and their parents, as well as the relationship between these parental indicators with those of their children. A total of 91 people were included in the study — parents and their children, 30 of whom (33%) were diagnosed with JIA. In total, 67% of parents and 27.5% of children were overweight (with JIA — 56.7 and 13.3%, respectively), in 80% of children with overweight, their parents also had it. The authors found a moderate association between total fat intake (Cramer's V test=0.254; p=0.037) and a weak association between intake of saturated fatty acids (Cramer's V test=0.219; p=0.050) and cholesterol intake (Cramer's V test=0.234; p=0.025) between parents and their children. High prevalence of dyslipidemia was observed in both parents (82.4%) and children (83.5%). A weak association was found between triglyceride levels in parents and their children (Cramer's V test=0.238; p=0.024), but no association was found between physical activity levels of parents and their children. High prevalence of overweight and dyslipidemia observed in parents, as well as the increased fat intake by parents and their children with chronic rheumatic diseases, indicate the importance of correcting the nutrition of these patients with the active involvement of their families in nutrition education programs [27].

The influence of maternal nutrition during pregnancy and child nutrition in the first year of life on the risks of developing juvenile idiopathic arthritis

E. Kindgren et al. in a 2019 study investigated the possible influence of maternal diet during pregnancy on the subsequent development of JIA. In a cohort of 15,740 newborns, the authors collected data on maternal diet, including fish consumption fish consumption, and obtained blood samples from mothers during pregnancy, as well as from their children at birth and at different ages. Sixteen years after the study began, JIA was diagnosed in 42 children, of whom 11 had antinuclear antibodies. Heavy metal analyses in cord blood were performed in all 42 patients who subsequently developed JIA and in 40 age- and gender-matched controls. It was found that maternal fish consumption more than once a week during pregnancy, as well as by the child himself during the first year of life, was associated with an increased risk of developing JIA ($p < 0.001$) and the presence of antinuclear antibodies ($p < 0.001$). Levels of aluminum (Al), cadmium (Cd), mercury (Hg), and lithium (Li) in cord blood were significantly higher in the group of children with JIA than in the control group. All children who were found to have antinuclear antibodies ate fish more than once a week during the first year of life. In patients with antinuclear antibodies, the levels of Al ($p < 0.001$), Cd ($p=0.003$), and Li ($p < 0.001$) in cord blood were significantly higher than in the control group. The frequency of maternal fish consumption during pregnancy correlated with the concentrations of Cd ($p=0.003$), Li ($p=0.015$), and Hg ($p=0.011$) in cord blood. Based on the results obtained, the authors conclude that moderate exposure to heavy metals associated with fish consumption during pregnancy and early childhood may affect the immune system, leading to the production of antinuclear antibodies and the development of JIA [28].

T. Hyötyläinen et al. in a 2024 study examined breast milk lipid composition in those mothers whose children later progressed to one or more immune-mediated diseases later in life, including 9 children with JIA, compared with breast milk lipid composition in mothers of healthy children. It was shown that maternal age, BMI, diet, and exposure to perfluorinated alkyl substances (PFASs) had a marked impact on breast milk lipid composition, with greater changes observed in the milk of those mothers whose children later developed autoimmune diseases. The authors observed features of breast milk lipid composition in mothers whose children later developed autoimmune diseases. However, due to the small number of study participants with each individual disease, they were all combined into one group, and differences in breast milk lipid composition in mothers of children with JIA compared to mothers of healthy children or children with other autoimmune diseases were not studied in this research [29].

JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

Juvenile systemic lupus erythematosus (JSLE) is a chronic immune/inflammatory disease with various clinical manifestations depending on the affected organs or systems, which in children and adolescents, compared with adult patients, usually proceeds more severely. M.C. Caetano et al. in the 2009 study mentioned above in the section on JIA, also assessed the diet of 22 children and adolescents with JSLE (3 males, 19 females, aged 9 to 20 years, mean age 16.5 years) and compared it with the clinical and anthropometric characteristics of the patients, as well as with the drugs used in their treatment. Among patients with JSLE, 68.2% had a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) >4. Malnutrition was found in 4.3% of patients with JIA, and obesity was present in 18.2%. In patients with JSLE, excess energy intake was noted in 13.6%, excessive protein intake — in 86.4%, and excessive lipid intake — in 36.4% of cases. Low iron intake was found in 50%, low zinc intake — in 86.4%, and low vitamin A intake — 95.2% of patients with JSLE. As in patients with JIA, no significant association was found between food intake, disease activity, and nutritional status in patients with JSLE included in this study [20].

S.G.L. da Silva et al. in 2018 published the results of a randomized controlled trial of the effect of nutritional intervention on lipid metabolite biomarkers associated with cardiovascular disease risk and their changes over time in patients with JSLE. The study included 31 adolescent girls aged 10 to 19 years who had been diagnosed with JSLE at least six months earlier. Patients were randomly assigned to the intervention group (15 patients, mean age 15.7±2.9 years) and the control group (16 patients, mean age 15.3±2.3 years). The mean disease duration, disease activity indices SLEDAI-2K and SLICC/ACR-DI did not differ significantly between the groups. Participants in the experimental group received oral and written nutrition guides once a month for 9 months. The intervention included the following steps: general orientation towards dietary behavior; ideas about healthy eating based on meal rotation; emphasis on adequate intake of carbohydrates and fats, including different types of fats, and attention to food labels; orientation towards adequate intake of salt, sugar, diet and light foods; qualitative changes in nutrition with an emphasis on fruits and vegetables (antioxidants), sea fish (ω-3) and intake of soluble and insoluble fiber; orientation towards diet and lifestyle, active leisure on weekends, and participation in parties and other events. After 9 months, the authors found a significant reduction in intake of calories (p=0.017), carbohydrates (p=0.030), total fat (p=0.020), saturated fat (p=0.013) and trans fat (p=0.012) in the study group compared with the control group. The activity of the high-density lipoprotein (HDL)-associated enzyme paraoxonase-1 by the end of the study was also significantly higher in the experimental group (p=0.021), indicating an improvement in HDL function and, as a result, a reduction in cardiovascular disease risks. In the control group, on the contrary, a significant increase in the level of low-density lipoproteins (HDL) was observed over time compared with the experimental group (p=0.018). The obtained data indicate that a rational diet in JSLE can help protect young patients from the premature atherosclerosis, the risks of which in JSLE are significantly higher than in the general population [30].

T.O. Abad et al., also in 2018, in the same group of 31 patients with JSLE, studied changes in body composition and assessed the association of total fat mass with clinical parameters. During the study period, the control group showed an increase in total fat mass by an average of 3.7 kg (p=0.013) and appendicular fat mass by 0.36 kg/m2 (p=0.007), while in the main group, no significant changes were observed in either total fat mass (p=0.446) or appendicular fat mass (p=0.494) over 9 months. Thus, 9-month diet therapy in patients with JSLE improved their eating habits and protected them from excessive body mass and fat deposits. However, the study did not reveal any association between total fat mass and physical activity, disease activity, or glucocorticoid use in either group [31].

In the 2020 study by L. Pereira et al., mentioned above in the section on JIA, the authors assessed the association between BMI, diet, physical activity, and lipid metabolite biomarkers in children and adolescents with various chronic rheumatic diseases, including JIAS, and their parents. Of the 91 patients included in the study, 41 (45%) were diagnosed with JIAS, 41.5% of whom were overweight, which was also observed in 65.9% of their parents. The data on the identified association between intake of total fat, saturated fat and cholesterol by parents and intake of these nutrients by their children are presented above in the section on JIA. However, it is worth noting separately that patients with JISC received a significantly higher dose of glucocorticoids than patients with JIA, and their use was associated with the presence of dyslipidemia (p=0.003), changes in the levels of LDL (p=0.017), HDL (p=0.043) and triglycerides (p=0.002) [27].

M.L.P Moreira et al. in 2021 evaluated fiber intake and its relationship with cardiovascular risk factors in 52 adolescents with JSLE (4 boys, 48 girls, mean age 16.7±1.5 years). The most common comorbidities identified were arterial hypertension (48%; n=25), dyslipidemia (44.2%; n=23), obesity (13.5%; n=7), and hyperglycemia (9.6%; n=5). Inadequate fiber consumption was observed in 61.5% of patients (n=32). Mean waist circumference (81.4 cm vs. 75.5 cm; p=0.02), waist-to-height ratio (0.51 vs. 0.47; p=0.02), and systolic blood pressure (122.1 mmHg vs. 114.8 mmHg; p=0.03) were higher in

those with low fibre intake. Among the assessed cardiovascular risk factors, waist-to-height ratio showed a significant negative correlation with fiber intake (r=–0.3; p=0.04). That is, the higher the fiber intake, the lower the waist-to-height ratio. Thus, low fiber intake in adolescents with JSLE is associated with higher levels of abdominal obesity and, consequently, with an increased risk of cardiovascular disease. Therefore, it is of utmost importance to assess and monitor the nutritional status of patients with JSLE and to develop strategies to promote adequate fiber and other nutrient intake [32].

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is a rare autoimmune disease characterized by systemic inflammation, skin rashes and muscle inflammation, as well as loss of muscle mass, symmetrical weakness of proximal muscle groups, decreased physical performance and increased fatigue. M.Y. Solis et al. in 2016 published the results of a randomized placebo-controlled trial of the efficacy and safety of dietary supplements with creatine (methylguanidine-acetic acid is an amine compound found in food, especially in meat, and endogenously synthesized from amino acids, capable of improving functional indicators in healthy individuals, children with muscular dystrophy and adult patients with idiopathic inflammatory myopathies). Creatine was administered at a dose of 0.1 g/kg/day for 12 weeks to 15 patients with JDM (10 females, 5 males, aged 7–21 years) who had been on stable therapy for at least 8 weeks and were receiving no more than 40 mg prednisolone per day. Twelve weeks of creatine supplementation in patients with JDM were well tolerated and did not cause any adverse effects, but the treatment did not affect muscle function, muscle phosphocreatine content, or contribute to any other therapeutic effect. These data suggest that the beneficial effects of this supplement previously demonstrated in adults with idiopathic inflammatory myopathies are not replicated in patients with JDM, but may be related to the small number of participants in this study. Larger studies are needed to clarify the feasibility of creatine supplementation in children with JDM [33].

L. Pereira et al. in the 2020 study mentioned above in the sections on JIA and JSLE assessed BMI, diet, physical activity, and lipid metabolite biomarkers in parents of children and adolescents with JIA, JSLE, and JDM, and the relationship between these parental indicators and their children's indicators. A total of 91 people were included in the study — parents and their children, 20 of whom (22%) were diagnosed with JDM, 20% of whom were overweight, that was noted in 70% of their parents. The associations found between total fat intake, saturated fat intake, and cholesterol intake between parents and their children are presented above in the section on JIA, and the associations between glucocorticosteroid use (which were prescribed at the same frequency in JDM as in JSLE and, as in JSLE, were associated with the presence of dyslipidemia) and changes in LDL and HDL levels, as well as triglycerides levels are presented in the section on JSLE [27].

IGA VASCULITIS

IgA vasculitis is a systemic vasculitis that is most common in childhood and is characterized by non-thrombocytopenic purpura accompanied by joint pain and swelling, abdominal pain, hematuria and proteinuria. L.J. Xiong et al. in a 2019 randomized controlled trial studied the clinical effect of alanyl-glutamine-enriched nutritional support in the treatment of children with abdominal form of IgA vasculitis who required nutritional support. Patients were randomly divided into a control group receiving nutritional support without alanyl-glutamine (n=118) and a nutritional support group enriched with alanyl-glutamine (n=107). According to disease severity, intravenous glucocorticoids were used in both groups. Other treatments were the same in both groups. Two groups were compared in terms of the length of hospital stay, frequency and duration of intravenous glucocorticoid therapy, frequency of symptom recurrence during hospital stay, frequency of total parenteral nutrition, rate of weight loss, and frequency of fasting for more than 5 days. All patients were followed up for 3 months after discharge to monitor symptom recurrence. There were no

significant differences in the length of hospital stay, total parenteral nutrition, and frequency of fasting for more than 5 days between the two groups (p >0.05). Compared with the fortified nutritional support group, the control group showed a significant increase in the frequency and duration of intravenous glucocorticoid administration, symptom recurrence rate, and weight loss rate (p <0.05). After 3-month follow-up, all children returned to normal feeding, and the recurrence rate of abdominal symptoms in each group was less than 20%. The most common symptom was abdominal pain, followed by vomiting and bloating. No gastrointestinal bleeding was observed. All symptoms resolved after symptomatic treatment. No significant difference was found in the recurrence rate of abdominal symptoms between the two groups (p=0.693) [34].

L.H. Shang et al. in a 2021 study evaluated different enteral feeding regimens in children with abdominal form of IgA vasculitis who were hospitalized between August 2013 and August 2018. According to the starting time of enteral nutrition after abdominal pain relief, the children were divided into three groups: <24 hours (n=68), 24-48 hours (n=64), and 48–72 hours (n=60). According to the type of enteral nutrition, they were divided into another three groups: amino acid-based formula (n=53), extensively hydrolyzed lactoprotein formula (n=67), and normal diet (n=72). The recurrence rate of clinical symptoms and degree of satisfaction among family members were compared between groups. Based on the retrospective analysis, 166 children with abdominal form of IgA vasculitis were enrolled in a prospective study. All patients were given extensively hydrolyzed lactoprotein formula after abdominal pain relief. According to the feeding time after abdominal pain relief, they were divided into three groups: <24 hours (n=52), 24–48 hours (n=59), and 48–72 hours (n=55). The three groups were compared in terms of the recurrence rates of abdominal pain, rash, and hematochezia, the rate of use of parenteral nutrition and intravenous glucocorticoids, and the incidence rate of weight loss at discharge. The retrospective analysis showed that the children who were given extensively hydrolyzed lactoprotein formula for enteral nutrition at 24–48 hours after abdominal pain relief had a lower recurrence rate of clinical symptoms and the highest degree of satisfaction among their family members (p <0.0167). The prospective study showed that the children who were given extensively hydrolyzed lactoprotein formula for enteral nutrition at 24–48 hours after abdominal pain relief had lower recurrence rates of rash and abdominal pain, a lower rate of use of parenteral nutrition, and a lower incidence rate of weight loss at discharge (p <0.05). Thus, according to both retrospective and prospective studies, in children with abdominal IgA vasculitis, it is advisable and effective to start feeding with hydrolyzed milk formula based on lactoprotein 24–48 hours after the relief of abdominal pain [35].

D.H. Yin et al. in a 2021 study assessed the effect of animal protein in the diet on the risk of IgA vasculitis recurrence in 121 children who were hospitalized between October and December 2020. All children were assigned the same diet (animal proteins could be added to the diet 1 week after the onset of skin rash). Follow-up was performed at the outpatient service for half a year. According to the presence or absence of animal protein intake, the children were divided into an observation group (65 children) and a control group (56 children). The incidence of IgA vasculitis recurrence, times of skin rash recurrence and the incidence of kidney injury were compared between the two groups. According to the presence or absence of recurrence, the children were divided into a recurrence group (32 children) and a non-recurrence group (89 children). There was no significant difference between the observation and control groups in the incidence rate of IgA vasculitis recurrence, times of skin rash recurrence, and incidence rate of kidney injury (p >0.05). There was no significant difference in the daily intake of animal protein between the recurrence and non-recurrence groups (p >0.05). The multivariate logistic regression analysis showed that presence of kidney injury at initial onset, respiratory infection after treatment, and lack of exercise control were independent risk factors for the recurrence of IgA vasculitis in children (p <0.05). No significant association between animal protein intake and the recurrence of IgA vasculitis was found [36].

L. Wang et al. in a 2021 randomized controlled trial examined the effects of dietary guidance on the treatment of IgA vasculitis. Thirty children with IgA vasculitis (16 boys, 14 girls, mean age 6.9±0.5 years) followed a traditional restrictive diet for IgA vasculitis. They were prohibited from eating fish, shrimp, meat, eggs, milk, vegetables, fruits and spices, as well as raw, cold, hard and other stimulating foods. Three meals a day included rice, noodles, steamed bread, porridge and some salt. Patients were advised to drink warm boiled water. When the abdominal pain had disappeared and no new rash elements had appeared within 7 days, vegetables were added to the diet, usually in the following order: potatoes, cabbage, sweet potatoes, green vegetables, cauliflower, white cabbage, cucumber, etc. Also in this case, a small amount of fruit was added to the food in the following order: banana, apple, watermelon, pear, etc. The interval between adding two kinds of vegetables or fruits should be at least 5 days, and vegetables and fruits can be added in turn. After no new rash occurs in 1 month, a small amount of eggs and milk can be added. If the disease does not recur for 2 months after adding eggs and milk, a small amount of meat can be added to the diet. If skin rash, abdominal pain, and other recurring symptoms appear while expanding the diet, it is necessary to stop taking the added product and resume taking it after the situation stabilizes. Another 30 randomly selected children with IgA vasculitis (12 boys, 18 girls, mean age 6.95±0.47 years) formed a group of a dietary program. It was based on a conventional diet, which was adjusted through the results of the nutritional analysis, the recommended nutrient intake of children and the dietary norm, and the results of allergen monitoring. Children with cow's milk protein allergy were supplemented with amino acid-based formula, while children without allergy were supplemented with extensively hydrolyzed lactoprotein formula. Nutritional testing was conducted throughout the dietary adjustment process, including the addition of vegetables, fruits, eggs, milk, and meat. An additional 30 children with bronchitis, matched by gender and age (13 boys, 17 girls, mean age 6.9±0.6 years) and not suffering from food allergy or intolerance, were included in the comparison group. Children in the control group ate as usual without restrictions. No significant differences were found in the height, weight, and BMI of children in the three groups upon admission ($p > 0.05$). In addition, no significant differences were found in the indices of red blood cells, hemoglobin, serum albumin, serum prealbumin, calcium, and iron content in the three groups ($p > 0.05$). The study showed that the time of complete disappearance of skin rash in children in the experimental group was significantly shorter than in children in the group receiving a traditional restrictive diet (11.3±1.1 days versus 18.5±1.8 days, $p < 0.05$). Recurrent rash was observed in 6 children in the experimental group (20%), which was significantly less than in the group receiving a traditional restrictive diet (14 children (46.7%), $p < 0.05$). In the group of children receiving a traditional restrictive diet, kidney injury was observed in 19 children, including 13 children with isolated hematuria, and in 6 children hematuria was combined with proteinuria. In the group with the recommended diet, kidney injury was significantly less common — in 11 children from the group (8 children had isolated hematuria and 3 children had hematuria combined with proteinuria), 36.7% versus 63.3% ($p < 0.05$). In the traditional restrictive diet group, levels of nutrient intake and the actual/recommended percentage were lower, while the overall nutrient intake level of recommended diet group was higher and basically corresponded to the normal intake level. In addition, the actual intake and actual/recommended percentage of nutrients in the recommended diet group were significantly higher than those in the traditional restrictive diet group ($p < 0.05$). Thus, individual dietary recommendations may both improve nutrient and protein intake of children with IgA vasculitis and reduce the incidence the relapse of rash and renal complications [37].

KAWASAKI DISEASE

Kawasaki disease is an acute systemic vasculitis that most commonly affects children under 5 years of age. The disease is characterized by fever, bilateral conjunctival hyperemia, cervical lymphadenopathy, oropharyngeal mucosal changes, erythematous rash,

and erythema and edema of the distal extremities. It is the leading cause of acquired heart disease in children in most developed countries. Because Asian ethnicity is one of the main risk factors for Kawasaki disease, there are several theories of reasons for the differences in its ethnic prevalence. Theories suggesting genetic differences between populations are prevalent and are areas of active study by numerous research groups. At the same time, differences in diet between Eastern and Western populations are often presented as the cause of certain ethnic differences in the susceptibility to cardiovascular disease and cancer in adults. Surprisingly, dietary differences as a possible cause of the heterogeneous prevalence of Kawasaki disease among different ethnic groups had never been considered until 2013. At that time, M.A Portman first conjectured that the development of Kawasaki disease could be associated with increased soy consumption. This was based on studies that revealed the role of specific immune Fcγ receptors in the pathogenesis of Kawasaki disease and in its response to intravenous immunoglobulin therapy. The functions of Fcγ receptors are regulated by isoflavones contained in soy, in particular genistein, which are involved in the pathogenesis of Kawasaki disease by modulating the function of Fcγ receptors and disrupting the balance between activation and inhibition of inflammatory responses. Asian children consume significantly more isoflavones than Caucasian children of comparable age. Asian families usually add tofu to breastfeeding or formula feeding, starting at 4–6 months. This is exactly the age when Kawasaki disease begins to occur significantly more often than in children in the first six months of life. Moreover, infants fed tofu have higher concentrations of isoflavones in plasma and urine than adults consuming soy (who are almost never affected by Kawasaki disease) [38].

The hypothesis of M.A Portman et al. was confirmed in his subsequent 2016 study, which examined the dietary intake of soy and isoflavones immediately before the onset of the disease in a group of 181 children with Kawasaki disease (17% Asian, 61% boys, mean age 4.0 ± 3.7 years), compared with a control group of 193 healthy children (11% Asian, 51% boys, mean age 5.2±4.2 years). Surveys of mothers on soy consumption during pregnancy and breastfeeding revealed no significant differences between groups. More than half of the children in both groups did not receive soy, but mean isoflavone intake was more than twice as high in children with Kawasaki disease compared to the control group, especially among Asian children. The authors found a significantly increased risk of developing Kawasaki disease in children with total isoflavone (odds ratio (OR) 2.33; 95% confidence interval (CI) 1.37–3.96) and genistein (OR 2.46; 95% CI 1.46–4.16) intake compared with children who did not consume soy. A significantly increased risk of developing Kawasaki disease was observed in Asian children with the highest isoflavone intake (total isoflavones: OR 7.29; 95% CI 1.73–30.75; genistein: OR 8.33; 95% CI 1.92–36.24) compared with European children. Because Asian populations typically consume soy products in combination with other foods that are more common in their diets than in European populations, the authors further analyzed the association between noodle, white rice, and other grain consumption and Kawasaki disease. No relationships were found, supporting the hypothesis that Kawasaki disease is associated with soy products rather than with other foods commonly present in the Asian diet. Furthermore, dietary isoflavone intake in childhood, rather than maternal isoflavone intake during pregnancy and breastfeeding, is associated with the risk of developing Kawasaki disease in an ethnically diverse US population [39].

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease characterized by recurrent attacks of systemic inflammation lasting 1–3 days, manifested by fever, abdominal pain, joint pain, chest pain and skin rash. R.M.K. Ekinci et al. in a 2020 study assessed the impact of diet preference to the disease course in 74 children (30 boys, 44 girls, mean age 14.6±2.82 years) with FMF. A statistically significant (p=0.022)

higher rate of complete response to colchicine therapy was found in patients who preferred less salty and less fatty foods. Thus, it was shown that a low-salt and low-fat diet may be an additional option in the treatment of children with FMF. Further studies are needed to clarify the role of a low-salt and low-fat diet in the pathogenesis of FMF [40].

Y. Kazem et al. in a 2021 study examined the effects of anti-inflammatory diet on clinical manifestations and cognitive functions in 73 patients (39 males, 34 females, aged 7–24 years) with FMF. In addition to their usual doses of colchicine, patients followed an anti-inflammatory diet (rich in fresh vegetables and fruits, low in saturated and unsaturated fats and carbohydrates, low in food additives, sugar, fast food and semi-finished products) with additional curcumin intake (10 mg per day), flaxseed rich in omega-3 PUFA (2 teaspoons per day), and vitamin D (4000 IU per day) for 6 months. The results showed statistically significant improvements in clinical presentation in terms of duration, frequency and severity of attacks (p=0.05), subjective well-being (p=0.05), cognitive functions (p=0.05) and school performance (p=0.01). A decrease in CRP the levels (p=0.01) and an increase in the level of vitamin D (p=0.01), deficiency of which was observed in all patients at the time of inclusion in the study, were also noted. The potential of anti-inflammatory diet in terms of improving the clinical picture, cognitive functions and overall health of patients with FMF was shown. However, the authors recommend that the findings be confirmed by a randomized controlled trial [41].

CONCLUSION

The quality and quantity of studies investigating the role of diet in the development and treatment of rheumatic diseases in children remain insufficient. More research is needed before any specific diet can be widely recommended for children with JIA and other rheumatic diseases. Because the relationship between nutrition and rheumatic diseases is significant and bidirectional, dietitians should be knowledgeable about JIA and other rheumatic diseases and work closely with pediatric rheumatologists and other healthcare professionals. This is necessary to comprehensively improve the health of young patients and maintain their normal physical development despite the negative impact of chronic inflammatory disease and its aggressive treatment. In addition, pediatric rheumatologists would greatly benefit from having a dietitian on their team to promptly identify nutritional problems in patients and to suggest the best individual diet for each patient.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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PERMEABILITY OF THE INTESTINAL EPITHELIAL BARRIER: EVALUATION CRITERIA, ROLE IN THE PATHOGENESIS OF CELIAC DISEASE

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ABSTRACT. The main structures responsible for maintaining the integrity of the intestinal barrier are tight junctions. Evidence of their role was obtained using electron microscopy and electrophysiology. A new and promising direct method for assessing the intestinal barrier function is confocal laser endomicroscopy. There is a growing interest in indirect assessment of the integrity of the mucosa using potential biomarkers. The levels of β-zonulin in stool and serum, and claudin levels in the blood are studied in various diseases. The article reflects the literature data on studies examining the possibilities of non-invasive methods for assessing the state of the epithelial barrier in the diagnosis of celiac disease and monitoring compliance with a gluten-free diet by the patient. Despite a large number of studies demonstrating increased intestinal permeability in celiac disease, the question of the place of dysfunction of the epithelial barrier of the small intestine in the pathogenesis of celiac disease remains relevant. The question of whether the barrier dysfunction is primary or a consequence of celiac disease itself has not yet been resolved.

KEYWORDS: *claudin, zonulin, confocal laser endomicroscopy, epithelial barrier, intestinal permeability, celiac disease*

ПРОНИЦАЕМОСТЬ ЭПИТЕЛИАЛЬНОГО БАРЬЕРА КИШКИ: КРИТЕРИИ ОЦЕНКИ, РОЛЬ В ПАТОГЕНЕЗЕ ЦЕЛИАКИИ

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РЕЗЮМЕ. Основными структурами, отвечающими за поддержание целостности кишечного барьера, являются плотные контакты. Доказательства их роли получены с помощью электронной микроскопии и электрофизиологии. Новым и перспективным прямым методом оценки барьерной функции кишечника является конфокальная лазерная эндомикроскопия. Растет интерес к косвенной оценке целостности слизистой оболочки с помощью потенциальных биомаркеров. Изучают уровни зонулина в стуле и в сыворотке крови, уровни клаудинов в крови при различных заболеваниях. В статье отражены литературные данные об исследованиях, посвященных изучению возможности неинвазивных методов оценки состояния эпителиального барьера при диагностике целиакии и контроля за соблюдением безглютеновой диеты пациентом. Несмотря на большое количество исследований, демонстрирующих повышенную проницаемость кишечника при целиакии, актуальным остается вопрос о месте в патогенезе целиакии дисфункции эпителиального барьера тонкой кишки. Вопрос о том, является ли дисфункция барьера первичной или следствием самой целиакии, все еще не решен.

КЛЮЧЕВЫЕ СЛОВА: *клаудин, зонулин, конфокальная лазерная эндомикроскопия, эпителиальный барьер, кишечная проницаемость, целиакия*

The intestinal barrier is a complex system that provides highly selective protection of the internal environment of the body from external influences using both immune and non-immune mechanisms. The main structures maintaining the integrity of this barrier are tight junctions (TJs). Their importance has been confirmed by electron microscopy (EM) and electrophysiological studies. In the apical region of the epithelium there is an intercellular gap (around 90 Å) named *zonula occludens* or tight junctions, followed by the *zonula adherens* (gap of 200 Å), followed by the *macula adherens* or desmosomes (gap of ~240 Å) [1]. Recently, two types of TJ-regulated pores have been identified: high-capacity charge-selective pores that allow small ions and small uncharged molecules to pass through (the "pore" pathway), and large pores with low selectivity (the "leak" pathway) that are permeable to large ions and molecules regardless of charge. At the molecular level, the first pore is regulated by claudins and the latter by the tight junction proteins such as occludin and the *zonula occludens* (ZO) family [1].

Confocal laser endomicroscopy (CLE) is a modern direct method for assessing intestinal barrier function. Using a confocal probe equipped with a 488 nm laser, increasing gaps between epithelial cells (1), leakage of fluorescein into the intestinal lumen (2), and epithelial cell shedding (3) can be directly visualized after intravenous administration of fluorescein [2, 3]. This method has been used to study intestinal permeability in various conditions and has shown increased duodenal permeability upon exposure to food antigens [1, 4, 5].

Due to the labor-intensive nature and limited availability of direct tests for intestinal permeability both *ex vivo* and *in vivo*, there is growing interest in indirect methods for assessing mucosal integrity, including potential biomarkers, such as zonulin.

Zonulin, a 47 kDa human pre-haptoglobin, is similar to cholera toxin (zonula occludens toxin — ZOT). Zonulin is synthesized in the liver and enterocytes. It can be isolated from a membrane complex (claudin-occludin-guanylate kinase-like zonula occludens (ZO) proteins 1, 2, and 3), which forms tight junctions in the apical part of the intestinal epithelium [6–8]. Recently, zonulin has been considered as a family of structurally and functionally related proteins [1]. Secreted into the lumen of the gastrointestinal tract, zonulin stimulates protease-activated receptors (PAR) and epidermal growth factor receptors (EGFr), which induce the "opening" of epithelial junctions, increasing paracellular permeability, and allows molecules with a molecular weight of more than 3.5 kDa to cross the intestinal barrier [9].

In most studies, zonulin is determined in two biological environments: blood and stool [10]. Determination of zonulin in stool may indicate the rate of its production in enterocytes, and in the blood — the transport of this protein from the intestinal lumen to the submucosa, between intestinal epithelial cells [8, 9]. The half-life of zonulin in the blood varies and ranges from 4 minutes to 4 hours, which leads to a significant spread in concentration (from undetectable to very high) [10, 11]. Increased zonulin concentrations have been shown in various conditions, including celiac disease, type 1 diabetes mellitus, inflammatory bowel disease, obesity, schizophrenia, and others [9].

Two decades ago, increased zonulin protein concentration was shown in patients with active celiac disease by the group of Fasano. Gliadin induced release of zonulin by binding to CXCR3 and elevated permeability *ex vivo* in biopsies of healthy volunteers and patients with quiescent celiac disease. However, both the baseline permeability and permeability after the addition of gliadin were higher and the luminal zonulin release was more pronounced and prolonged in patients with celiac disease [1].

A recent study examined serum zonulin levels in children at risk for celiac disease starting 12 months before diagnosis compared to controls without celiac disease, and identified clinical factors that contribute to disease manifestation. Children with celiac disease showed a significant increase in zonulin levels for about 18 months (range 6–78) before diagnosis compared to children without the disease. A correlation was found between the number of antibiotic courses and the increase in zonulin levels in patients with celiac disease. The authors suggest that zonulin may be used as a biomarker for preclinical assessment of celiac disease in children at risk, and multiple antibiotic courses may increase their risk of developing the disease by increasing zonulin levels [12].

Another study determined reference values of fecal zonulin concentrations in children under 16 years of

age. It was statistically significant that zonulin levels in children with clinical manifestation of celiac disease were significantly higher than in healthy children and children who followed a gluten-free diet for 6 months. The authors suggest using zonulin levels as an additional tool for monitoring adherence to a gluten-free diet [13].

When comparing the amino acid composition of zonulin and its Zot active fragment, similarities in amino acids were found. An octapeptide (GGVLVQPG) was synthesized, named FZI/0, AT1001, and recently larazotide acetate corresponding to 8 amino acids of this fragment was also synthesized [1]. Larazotide acetate (LA) is a single-chain peptide that acts as a tight junction regulator to restore intestinal barrier function. The main function of LA is to act as an anti-zonulin receptor inhibitor to reduce zonulin-induced increases in increase in intestinal barrier permeability [14]. The mechanism of action of LA is thought to be associated with the redistribution and rearrangement of tight junction proteins and actin filaments to restore intestinal barrier function. Recent studies have shown that LA inhibits myosin light chain kinase, which likely reduces tension on actin filaments, thereby facilitating tight junction closure [14]. Currently, phase III clinical trials have been completed in which LA was administered orally to adult patients with celiac disease as an adjunct therapeutic to enhance the intestinal barrier function. The results of these studies are encouraging: the biological safety of LA has been confirmed. A greater reduction in intestinal symptoms was also shown in patients receiving LA in combination with a gluten-free diet compared to those following the diet alone. However, statistically significant differences in the lactulose to mannitol ratio compared with placebo group were not observed [15, 16]. Further studies are needed to clarify whether there are other mechanisms of action of LA on intestinal permeability and how it can be applied in clinical practice.

Claudins are integral transmembrane proteins that span the membrane bilayer four times. These proteins form structural and functional regions that include four transmembrane domains, two extracellular loops, one cytoplasmic loop, and N- and C-cytoplasmic domains. In the intestine, abnormalities of claudins 2, 3, 4, 7, 12, and 14 lead to impaired intestinal barrier function [17]. It is believed that changes in claudin levels play an important role in the pathogenesis of various diseases, including celiac disease [18–21].

The question of the nature of the epithelial barrier defect in celiac disease remains open. It may occur secondarily due to the inflammation localized in the lamina propria of the small intestine mucosa in the active form of the disease. The epithelial barrier defect may also be primary, since claudin levels are altered both in patients with quiescent celiac disease on a gluten-free diet and in relatives of patients who do not have this disease [22, 23].

Recently, V. Kumar et al. identified genes associated with celiac disease that define the barrier, providing genetic evidence for the importance of barrier function in the pathogenesis of the disease [8]. It is significant that the barrier function is maintained by a complex interaction of proteins, where the main structural elements are tight junction proteins: occludin, claudins, and scaffolding proteins such as ZO-1 [24]. Although structural changes in barrier function in celiac disease may be related to the composition of enterocyte tight junctions and epithelial transcytosis of gliadin peptides, the number of studies aimed at elucidating the mechanisms of these changes is insignificant [20, 25–28]. One recent study showed that monocytes obtained from patients with celiac disease are able to induce a barrier defect in intestinal epithelial cells [29].

In addition, despite the large number of studies showing increased intestinal permeability in celiac disease, the question of whether the barrier dysfunction is primary or a consequence of celiac disease itself remains relevant.

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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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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CRITERIA FOR CHOOSING ORTHODONTIC APPLIANCES IN CHILDREN 8–11 YEARS OLD WITH MALOCCLUSION AND TYPE 1 DIABETES MELLITUS

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ABSTRACT. ***Introduction.*** Type 1 diabetes mellitus (DM1) in children requires a special approach in orthodontic treatment, as the disease affects the condition of the tissues of the oral cavity and makes it difficult to correct malocclusion. The article discusses the criteria for choosing orthodontic equipment and methods of treatment for children with DM1, taking into account their metabolic characteristics. Metabolic disorders that lead to dry mouth (xerostomia), an increased risk of caries and periodontal diseases, as well as delayed tissue healing complicate the choice of orthodontic devices and require special attention to oral hygiene. ***The aim of the study*** was to determine the criteria for choosing orthodontic devices for patients aged 8–11 years with occlusion anomalies and DM1. ***Materials and methods.*** The study involved children aged 8–11 years: 17 patients with DM1 and 38 children without this disease. Clinical examination methods were used, such as questioning, examination, examination of the oral cavity and teeth, as well as the parotid soft tissues. ***Results.*** Patients with DM1, compared with children who do not have this disease, were more likely to experience discomfort caused by the pressure of orthodontic devices on the mucous membrane, which required an increase in the number of unscheduled visits and adaptation of therapeutic measures to the existing condition. To reduce the load on the tissues, the elements of the devices were alternately activated, which helped reduce the risk of complications. Special attention was paid to careful monitoring of glucose levels before starting treatment, which reduced the likelihood of complications, secondary infections and delayed tissue healing at the contact points of the device parts. ***Conclusion.*** Patients with DM1 often had changes in the color of the mucous membrane, bleeding gums and long-term non-healing wounds, therefore, it was recommended to use devices made of soft and elastic materials that minimally affected the soft tissues during support and provided comfortable wearing. It is necessary to avoid structures made of plastic with sharp edges that can injure the mucous membrane and regularly to check the condition of the gums and mucous membrane to prevent the development of periodontal diseases and caries. Orthodontic treatment of children with DM1 requires a carefully individualized approach, including interdisciplinary collaboration and the use of minimally invasive techniques. It is necessary to take into account the psychoemotional state of children with DM1, provide them with regular orthodontist supervision, and support from dental specialists. This approach will help minimize the risks of complications and ensure the successful outcome of orthodontic correction of malocclusion, improving the quality of life of patients and their families.

KEYWORDS: *type 1 diabetes mellitus, mucous membrane of the oral cavity, orthodontic treatment, malocclusion pathology, OT-orthodontic correctors, orthodontic devices*

КРИТЕРИИ ВЫБОРА ОРТОДОНТИЧЕСКОЙ АППАРАТУРЫ У ДЕТЕЙ 8–11 ЛЕТ С АНОМАЛИЕЙ ПРИКУСА И САХАРНЫМ ДИАБЕТОМ 1-ГО ТИПА

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РЕЗЮМЕ. ***Введение.*** Сахарный диабет 1-го типа (СД1) у детей требует особого подхода при ортодонтическом лечении, так как заболевание влияет на состояние тканей полости рта и затрудняет процесс коррекции аномалий прикуса. В статье рассмотрены критерии выбора ортодонтической аппаратуры и методы лечения детей с СД1, учитывающие их метаболические особенности. Нарушение обмена веществ, которое приводит к сухости во рту (ксеростомии), повышенному риску кариеса и пародонтальных заболеваний, а также замедленному заживлению тканей, усложняет выбор ортодонтических аппаратов и требует особого внимания к гигиене полости рта. ***Цель исследования*** – определение критериев выбора ортодонтических аппаратов для пациентов 8–11лет с аномалиями окклюзии и СД1. ***Материалы и методы.*** В исследовании участвовали дети в возрасте 8–11 лет: 17 пациентов с СД1 и 38 детей без этого заболевания. Использовались клинические методы обследования, такие как опрос, осмотр, исследование полости рта и зубов, а также околочелюстных мягких тканей. ***Результаты.*** Пациенты с СД1 по сравнению с детьми, у которых отсутствует данное заболевание, чаще испытывали дискомфорт, вызванный давлением ортодонтических аппаратов на слизистую оболочку, что требовало увеличения количества внеплановых посещений и адаптации лечебных мероприятий к существующему состоянию. Для уменьшения нагрузки на ткани проводилась поочередная активация элементов аппаратов, что способствовало снижению риска осложнений. Особое внимание уделялось тщательному контролю уровня глюкозы перед началом лечения, что снижало вероятность осложнений, присоединения вторичных инфекций и замедленного заживления тканей в местах контакта деталей аппарата. ***Заключение.*** У пациентов с СД1 часто наблюдались изменения цвета слизистой оболочки, кровоточивость десен и длительно незаживающие раны, поэтому рекомендовалось использовать аппараты, выполненные из мягких и эластичных материалов, которые минимально воздействовали на мягкие ткани при опоре и обеспечивали комфортное ношение. Нужно избегать конструкций, выполненных из пластмассы, с острыми краями, способных травмировать слизистую оболочку. Важно регулярно проверять состояние десен и слизистой оболочки, чтобы предотвратить развитие пародонтальных заболеваний и кариеса. Ортодонтическое лечение детей с СД1 требует тщательно индивидуализированного подхода, включающего междисциплинарное взаимодействие и использование минимально инвазивных техник. Необходимо учитывать психоэмоциональное состояние детей с СД1, предоставлять им регулярное наблюдение ортодонта, поддержку со стороны специалистов стоматологического профиля. Такой подход поможет минимизировать риски осложнений и обеспечит успешный результат ортодонтической коррекции аномалий прикуса, улучшая качество жизни пациентов и их семей.

КЛЮЧЕВЫЕ СЛОВА: *сахарный диабет 1-го типа, слизистая оболочка полости рта, ортодонтическое лечение, патология прикуса, ОТ-ортодонтические корректоры, ортодонтические аппараты*

INTRODUCTION

Type 1 diabetes mellitus (DM1) is a chronic autoimmune disease characterized by absolute insulin deficiency due to destruction of the β-cells in Langerhans pancreatic islets. The disease is most often diagnosed in childhood and adolescence, which makes it important to consider its impact on various aspects of health, including dental status and orthodontic correction of bite abnormalities.

Orthodontic treatment of children with type 1 diabetes mellitus requires a special approach due to complications related to metabolic changes. Diabetes mellitus leads to metabolic disorders, which affects the condition of the tissues of the oral cavity. Children with DM1 are susceptible to a number of changes in the oral cavity, such as xerostomia, an increased risk of developing caries, periodontal diseases and delayed wound healing of tissues in the oral cavity [1, 2]. This may later limit the specialist in the choice of appliances, complicate the process of orthodontic treatment, require a special approach and interdisciplinary interaction of clinicians. Diabetic microangiopathy, decreased blood flow in the oral tissues and impaired bone remodeling worsen the condition of the entire maxillofacial region, which makes treatment more complex and requires careful monitoring and adaptation of treatment methods. Modern research emphasizes the need to take into account the systemic characteristics of patients with DM1 to ensure successful orthodontic treatment and minimize the risk of complications.

It has been established that type 1 diabetes mellitus is one of the most common forms of diabetes in children and adolescents. In the United States, about 5% of all cases of diabetes are type 1, and, as a rule, this type of diabetes develops in childhood or adolescence [3].

According to the US Centers for Disease Control and Prevention, if incidence rate continues to increase, the number of children and adolescents with type 1 diabetes could increase by 65% by 2060. Even if the current trend continues, the incidence will remain significant, requiring special attention to preventive measures and raising awareness of the disease among parents and healthcare professionals [4]. In addition, there is an increase in the number of diabetic complications in children, including impaired immune system function and an increased risk of ketoacidosis. These factors significantly affect the quality of life of children and require

According to various Russian sources, the prevalence of type 1 diabetes among children in Russia has also increased significantly in recent years. On average, the incidence is 15–20 new cases per 100,000 children per year [5]. These rates may vary by region of the country, with higher incidence rates in certain areas, such as the Tula, Kemerovo, and Ulyanovsk regions.

According to the National diabetes register, there are more than 30,000 children and adolescents with type 1 diabetes in the Russian Federation, and the number of new cases continues to grow every year, with an average annual increase of 2.8. The disease is characterized by an acute onset with pronounced symptoms such as thirst, weight loss, and frequent urination. These data emphasize the importance of early diagnosis and high-quality monitoring of children at risk of developing diabetes, as well as the need to develop prevention and timely treatment programs.

In the North-West region of the Russian Federation, including St. Petersburg, the prevalence of DM1 among children is even higher than in other regions of the country. Studies show that the incidence of DM1 in the Northwestern Federal District (NWFD) is 15.66 per 100,000 children. This figure is the highest among all federal districts of the Russian Federation, which indicates the importance of monitoring and prevention in this region and requires attention to issues of diagnosis and provision of high-quality medical care to children suffering from this disease.

The increase in the incidence of DM1 in recent decades and the improvement in the prognosis of the disease lead to an increase in the number of children who require orthodontic treatment. However, despite the increasing attention to this issue, there is a lack of systematic data on the specific features of orthodontic care for children with DM1 [6].

Thus, type 1 diabetes mellitus in children is a serious problem that requires special attention to diagnosis, treatment and management of the disease. Global trends show an increase in the prevalence of this disease among children, which makes it an important topic for medical research and the development of

new approaches to treatment and prevention. DM1 in children and adolescents not only affects metabolism, but can also significantly impact the development of dentofacial anomalies (DFA). Numerous studies show that predisposition to DFA in children with DM1 may be associated with genetic and epigenetic factors [7].

In DM1, growth retardation is also common, which leads to disturbances in the formation of the jaws and teeth [8].

Increased susceptibility to periodontal diseases in DM1 also affects the development of DFA. Periodontitis can cause gum recession and loss of dental tissue at an early age, which in turn leads to disruption of the anatomy of the stomatognathic system. Scientific studies conducted in 2015–2024 discussed the high prevalence of periodontal diseases in children with diabetes and their association with DFA [9–11].

Chronic hyperglycemia, characteristic of DM1, can lead to impaired tooth mineralization and decreased tooth strength. This increases the risk of caries and other dental diseases that may contribute to the development of anomalies. Many studies emphasize the relationship between glucose levels and the condition of tooth enamel [12]. It has also been established that changes in the composition and properties of oral fluid affect tooth mineralization [13].

AIM AND TASKS

The aim of this study is to analyze the characteristics of orthodontic treatment of children with DM1, identify specific problems and develop recommendations for optimizing orthodontic treatment approaches in this group of patients.

Tasks

1. Assess the condition of the oral cavity and the stomatognathic system in children with DM1.

2. Identify common malocclusion among this category of patients.

3. Study the impact of DM1 on the course and results of orthodontic treatment.

4. Compare the characteristics of orthodontic treatment of children with DM1 to control group without this disease.

5. Develop recommendations for orthodontists on the management of patients with DM1.

MATERIALS AND METHODS

The study involved patients of a dental clinic who had visited an orthodontist for an initial consultation. Based on the results of the survey (filling out a health questionnaire), a control group was determined, which did not include patients with an established diagnosis of DM1. The first group included 38 patients aged 8–11 years. The second group consisted of 17 patients of the same age with an established diagnosis of DM1. All patients sought orthodontic treatment.

RESULTS

When identifying complaints from patients (their legal representatives) of the second group, compared to the control group, not only the main complaint about the presence of malocclusion was identified, but also complaints about *dry mouth* (*xerostomia*). The presence of xerostomia in children and adolescents with diabetes is associated with disorder of salivation, which can be a consequence of both the disease itself and the use of hypoglycemic drugs. This situation is confirmed by the data of a study conducted in 2019 [14]. It indicates that most patients with DM1 have symptoms of dry mouth, which increases the risk of caries and infections.

Change in mucous membrane color. In children and adolescents with DM1, a change in the color of the mucous membrane is often observed. It can acquire a pale or yellowish tint, which is associated with disruptions in the microcirculation and metabolic processes. This is confirmed in one of the studies published in 2017 [15], which noted changes in the vascularization of the mucous membrane in diabetic patients.

Bleeding gums by tooth brushing.

Presence of long-term non-healing wounds, especially during professional dental cleaning, which may be associated with metabolic and vascular innervation disorders. Such processes indicate slowing healing of the oral mucosa as a result of chronic hyperglycemia.

During clinical check-up of patients in the second group, compared to the control group, it was found that the oral mucosa in patients had a number of characteristic changes.

Changes in the structure and color of the mucous membrane, presence of gingivitis. This is explained by the high risk of periodontal diseases in this group of patients. According to an analysis of scientific literature, including the results of one study conducted in 2016, the prevalence of gingivitis in children with DM1 is 75%, which is significantly higher than in healthy children. In turn, chronic gingivitis and susceptibility to infection can lead to loss of dental tissue and caries [16].

Some patients came to the clinic with symptoms of *stomatitis*. As is known, patients with DM1 are also at increased risk of infectious diseases of the oral mucosa, such as stomatitis and *candidiasis*. This is due to immune system disruption and increased salivary glucose level, which creates favorable conditions for the growth of pathogenic flora. Many studies have noted that up to 40% of patients with diabetes suffer from fungal infections [17].

There were no significant differences between the groups in terms of the severity of the anomaly. Patients in all groups had malocclusion to varying degrees that required orthodontic treatment. Basically, starting from the age of 8, the anomalies corresponded to codes K07.0, namely K07.2 Anomalies of dental arch relationships, then, after 10 years, they corresponded to the codes K07.2 Anomalies of dental arch relationships and K07.3 Anomalies of tooth position (according to ICD-10).

When assessing the impact of DM1 on the course and results of orthodontic treatment, it should be noted that in such patients, compared to the control group, a choice was more often made based on indications for the use of orthodontic devices made of medical soft and elastic materials (Fig. 1).

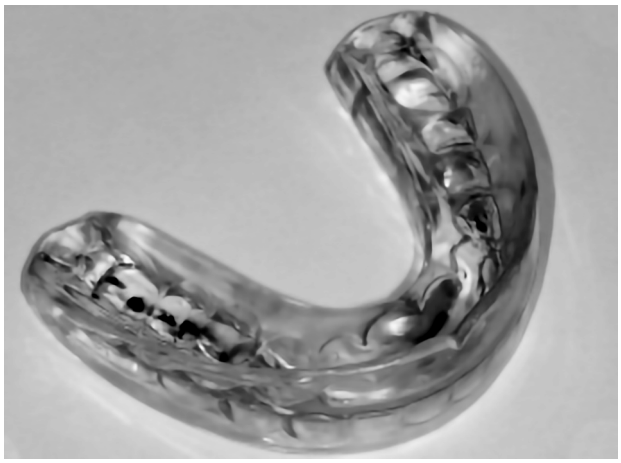


Fig. 1. The design of the OT-orthodontic corrector

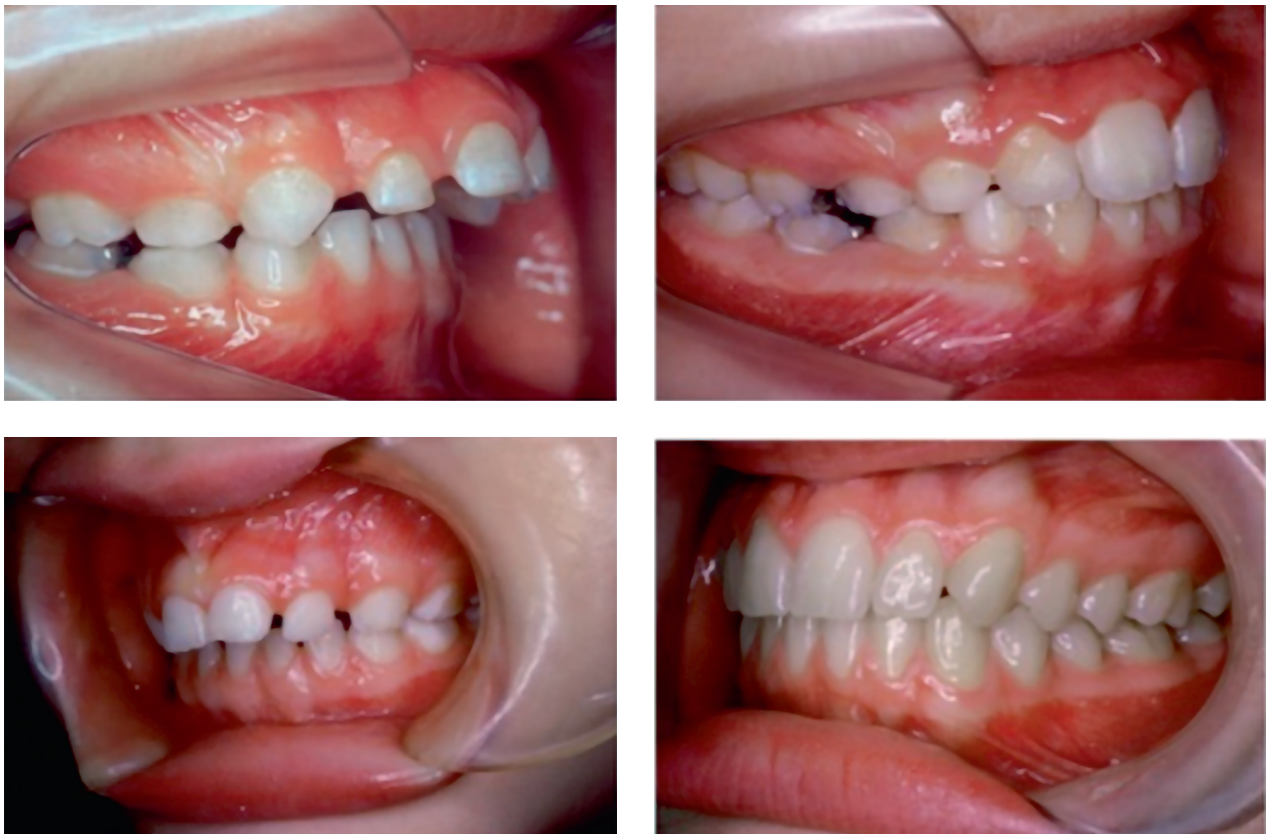
Рис. 1. Конструкция ортодонтического ОТ-корректора

During the control check-ups, when patients came for activation of the device, the condition of the mucous membrane and adjacent soft tissues, which the device exerts pressure on, was constantly assessed. In cases of using orthodontic appliances in two groups, identical in design with a screw and pushers, protractors, patients from the DM1 group more often came for additional visits, because some parts of the devices exerted pressure on the mucous membrane. Due to this, there were violations of the modes of use and activation of the orthodontic appliances in the DM1 group of patients compared to the control group and, as a consequence, an increase in the treatment time. The measures to activate the screw, pushers and other elements were not carried out simultaneously, but alternately or through visits for the same reasons — to ensure minimal impact on the tissues and enamel of the teeth. And therefore, when treating patients with DM1, the simplest in technical execution designs of orthodontic appliances were chosen, for example, such as OT-orthodontic correctors. Patients were more often recommended to undergo professional dental cleaning and received additional oral hygiene training. With such patients, when they came for control visits, conversations were held and recommendations were given in extremely friendly and solicitous tone, taking into account the above difficulties on their part during the treatment and their special psycho-emotional status.

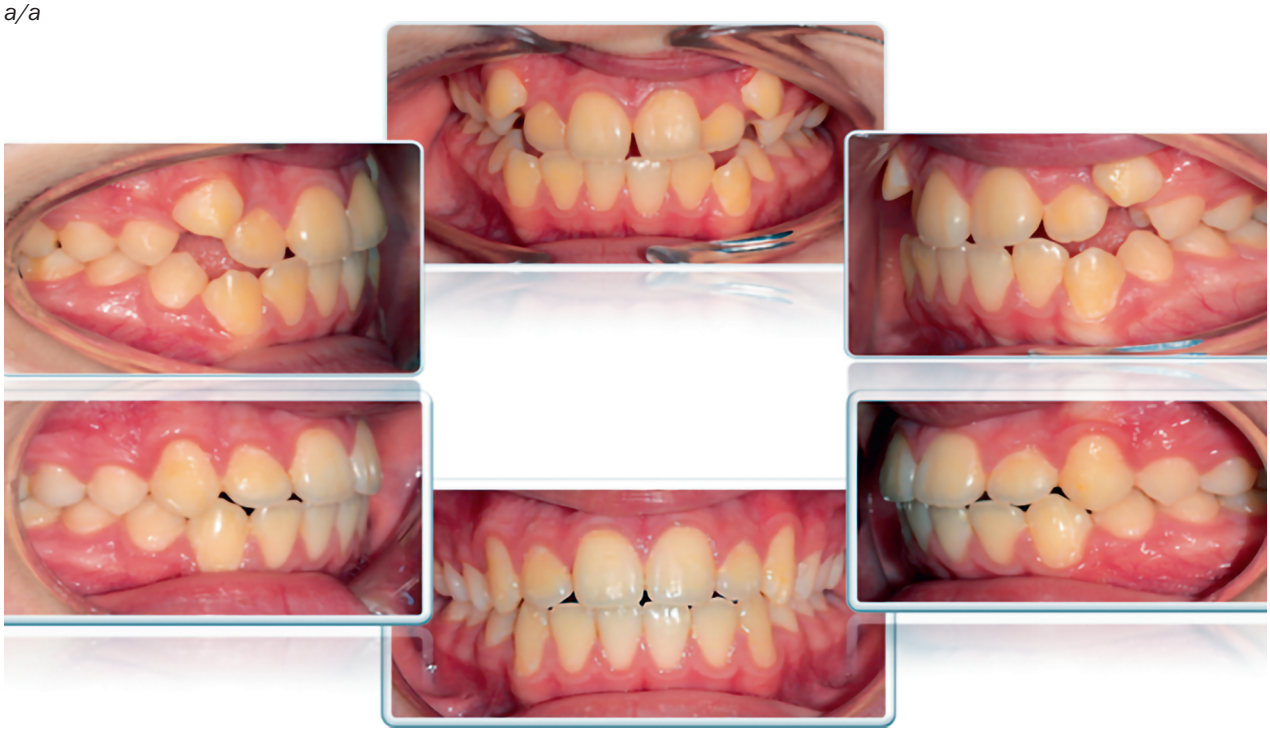
During the treatment of such patients, periodontal specialists were more often contacted to eliminate problems with soft tissues.

In addition to the recommendations for orthodontic treatment of such patients, it is necessary to conduct a general health assessment, namely: before starting orthodontic treatment, it is necessary to conduct a complete medical check-up, including blood glucose monitoring. This is important, since poor compensation of diabetes can lead to complications such as infections and delayed healing.

When choosing devices, it is necessary to take into account the condition of the gums and teeth. It is recommended to use appliances with minimal load to prevent tissue damage, since diabetes can lead to a decrease in the strength of teeth and tissues.



a/a



b/б

Fig. 2. The stages of application of orthodontic devices in the treatment of severe malocclusion: *a* — on removable devices; *b* — on fixed appliance

Рис. 2. Этапность применения ортодонтических аппаратов при лечении сложных аномалий окклюзии: *а* — на съемных аппаратах; *б* — на несъемных аппаратах

Type 1 diabetes mellitus has a significant impact on the oral tissues and skeletal system, making orthodontic treatment challenging. Research has shown that patients with diabetes have impaired alveolar bone remodeling and increased tooth mobility, which is associated with chronic hyperglycemia and metabolic disorders in the body. This is especially true for patients with poor glycemic control, as such patients are at increased risk of inflammatory diseases and unpredictable tooth movement during treatment. Therefore, complex orthodontic plans should be avoided, broken down into stages, and some limitations in tooth movement should be taken into account (Fig. 2, *a*, *b*).

Thus, orthodontic treatment in children with type 1 diabetes requires careful planning, including stabilization of blood sugar levels, monitoring of the condition of the gums and teeth with the use of the minimum possible physiological loads on the teeth to avoid complications and ensure successful treatment.

CONCLUSION

Clinical guidelines and protocols for orthodontic treatment of patients with malocclusion and type 1 diabetes mellitus, approved by the Russian Ministry of Health of the Russian Federation, describe various aspects of diagnosis, treatment and prevention [19–22]. The main focus is on how diabetes affects the stomatognathic system and the importance of taking this influence into account when planning orthodontic treatment.

Our study showed that it is necessary to determine the general health of patients with DM1. Before starting orthodontic treatment, it is necessary to conduct a thorough medical check-up of the patient for the presence of concomitant diseases associated with diabetes. It is necessary to develop an individualized treatment plan and adapt the choice of treatment method to the oral condition of patients with DM1. At the same time, minimally invasive techniques can reduce the risk of complications. When choosing appliances, preference should be given to devices that do not interfere with oral hygiene and do not have sharp edges in their design that can injure the mucous membrane. The increase in the duration of orthodontic treatment should be taken into account.

It is important to regularly check the condition of the gums and mucous membrane in this group of patients, especially during treatment, to prevent the development of periodontal disease and caries. Given the impact of chronic disease on the psychoemotional state of children, it is recommended to provide support and advice to help cope with stress and improve the quality of life.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Автор получил письменное согласие законных представителей пациентов на публикацию медицинских данных.

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LEVEL OF PHYSICAL FITNESS OF PRESCHOOL CHILDREN WITH DIFFERENT NUTRITIONAL STATUS

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ABSTRACT. ***Introduction.*** In the child population around the world, there is an increase in the prevalence of malnutrition, which has a negative impact on the physical development, functionality and physical performance of the growing organism. ***The purpose of the study*** is to identify the relationship between nutritional status and physical fitness of preschool children when performing the GTO complex. ***Materials and methods.*** The study involved 3,249 pupils of children's educational organizations in St. Petersburg aged 6.5 to 7.5 years. The study included somatometry (standing height and body weight) and performance of stage I exercises of the "VFSK GTO" (running at a distance of 30 m; shuttle running 3×10 m; standing long jump with a push with two legs and throwing a tennis ball at a target). The assessment of nutritional status was carried out in accordance with the standards of the WHO Growth Reference 2007. ***Results.*** It was revealed that 10.9% of study participants were underweight, and 24.0% were overweight and obese. Preschoolers, having fulfilled the standards of the "golden" badge, showed good development of speed qualities of physical fitness (distance running — 79.1% boys and 80.3% girls) and satisfactory formation of speed-strength indicators (jumping — 57.4% boys and 64 .5% girls; p=0.0004). Children are less prepared for motor coordination tests: 41.9% of boys and 62.5% of girls received a "golden" badge for throwing a ball at a target (p=0.0000); for shuttle running — 31.2% of boys and 64.5% of girls (p=0.0000). In all tests, children with a harmonious ratio of height and body weight are more successful, more often showing a valid result. Peers with obesity and malnutrition were less likely to perform well on tasks. ***Conclusion.*** Thus, the physical qualities of preschool children have great variability depending on gender and nutritional status, which must be taken into account when conducting physical education classes.

KEYWORDS: *children, preschoolers, physical development, malnutrition, obesity, physical education, GTO complex*

УРОВЕНЬ ФИЗИЧЕСКОЙ ПОДГОТОВКИ ДОШКОЛЬНИКОВ С РАЗЛИЧНЫМ НУТРИТИВНЫМ СТАТУСОМ

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РЕЗЮМЕ. ***Введение.*** В детской популяции во всем мире отмечается рост распространенности неполноценного питания, которое оказывает негативное влияние на физическое развитие, функциональные возможности и физическую работоспособность растущего организма. ***Цель исследования*** — выявить взаимосвязь нутритивного статуса и физической подготовленности детей дошкольного возраста при выполнении комплекса ГТО. ***Материалы и методы.*** В исследовании участвовали 3249 воспитанников детских образовательных организаций Санкт-Петербурга в возрасте от 6,5 до 7,5 лет. Исследование включало соматометрию (рост стоя и вес тела) и выполнение упражнений I ступени «ВФСК ГТО» (бег на дистанцию 30 м; челночный бег 3×10 м; прыжок в длину с места толчком двумя ногами и метание теннисного мяча в цель). Оценка нутритивного статуса проведена в соответствии со стандартами WHO Growth Reference 2007. ***Результаты.*** Выявлено, что 10,9% участников исследования имеют дефицит веса, а 24,0% — избыточную массу тела и ожирение. Дошкольники, выполнив нормативы «золотого» значка, показали хорошее развитие скоростных качеств физической подготовленности (бег на дистанцию — 79,1% мальчиков и 80,3% девочек) и удовлетворительное формирование скоростно-силовых показателей (прыжки — 57,4% мальчики и 64,5% девочки; p=0,0004). Хуже дети подготовлены к испытаниям на координацию движений: «золотой» значок получили за метание мяча в цель 41,9% мальчиков и 62,5% девочек (p=0,0000); за челночный бег — 31,2% мальчиков и 64,5% девочек (p=0,0000). Во всех испытаниях дети с гармоничным соотношением роста и массы тела более успешны, чаще показывая зачетный результат. Сверстники с ожирением и недостаточностью питания реже справлялись с заданиями. ***Заключение.*** Таким образом, физические качества у дошкольников имеют большую вариативность в зависимости от половой принадлежности и нутритивного статуса, что необходимо учитывать при проведении физкультурных занятий.

КЛЮЧЕВЫЕ СЛОВА: *дети, дошкольники, физическое развитие, недостаточность питания, ожирение, физическое воспитание, комплекс ГТО*

INTRODUCTION

The increasing prevalence of malnutrition and resulting health disorders in children and adolescents is a pressing problem for public health all over the world [1]. In 2016 the UN General Assembly formulated principles for an unprecedented fight against all forms of malnutrition for the next decade, which are reflected in the "Global Nutrition Monitoring Framework" [2]. Published domestic studies also highlight the significant prevalence of deviations in the physical development of the younger generation. They demonstrate how various medical and social factors influence nutritional status deviations in children [3–7].

Physical performance is one of the objective indicators of physical development, functional capabilities and health status of a growing human. It is possible to achieve the necessary and age-appropriate level of various physical qualities through physical exercises, taking into account sensitive periods of their formation [8–11]. A significant proportion of older preschool children are not ready to perform precise movements and solve motor tasks in extremely short time, and have reduced endurance to prolonged physical exertion [12–15]. It has been shown that children's motor coordination abilities can correlate with indicators of cognitive functions and, therefore, are an additional criterion of children's functional readiness for the beginning of systematic learning [16-18]. The authors have recently reported that there is a significant association between weight status categories and physical fitness in the pediatric population. Children and adolescents classified as underweight or overweight and obese had lower physical fitness scores than their normal-weight peers [19–22].

The physical fitness of children is predominantly assessed by a standard set of motor tests. In recent years, the All-Russian physical culture and sports complex "Ready for Labor and Defense" [Gotov k trudu i oborone] – "GTO"[1] has been actively introduced into the physical training of the younger generation. However, most publications on preparing children to perform the GTO complex are devoted to schoolchildren, since the authors consider tests are too difficult for preschoolers. This is justified by special orientation of test tasks only, they focus on the age-sex aspect without taking into account individual-typological characteristics of children [8, 12, 23]. From our point of view, it is possible to optimize physical training of preschool children by creating an information base and developing criteria that allow dosing physical loads with regard to the peculiarities of physical development.

AIM

To reveal the relationship between nutritional status and physical fitness of preschool children while performing the GTO complex.

MATERIALS AND METHODS

A cross-sectional, observational study was conducted on the basis of children's educational organizations ('CEOs') located in different districts of St. Petersburg. After obtaining informed consent from the children's legal representatives, 3249 children (1727 boys and 1522 girls) aged 6.5 to 7.5 years participated in the study. The study included weighing children on medical scales, measuring their standing height and performing GTO exercises.

Each participant's body mass index (BMI) was calculated by dividing the child's body weight (kg) by the square of standing height (m^2). Nutritional status was assessed according to WHO standards – WHO Growth Reference 2007 using Anthro Plus anthropometric calculator [24]. Nutritional status was classified according to age-sex BMI standards as malnutrition (MN; below the 5th percentile), undernutrition (UN; 5th–15th percentile), harmonious physical development (HPD; 15th–85th percentile), overweight (OW; 85th–95th percentile), and obesity (Ob; above the 95th percentile).

Physical fitness was assessed according to the results of the GTO first level tests. Taking into account the age-related physiology, we chose the following tasks: 30 m running (s), 3×10 m shuttle run (s), long jump from a place with a push of two legs (cm) and

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throwing a tennis ball at a target (number of hits from a distance of 5 m). Grading of results included categories: “gold”, “silver”, “bronze” and “fail” (when pupils failed to complete a task).

The obtained material was summarized in spreadsheets on Microsoft Excel platform and processed by generally accepted methods of statistical analysis using IBM SPSS Statistics package. Obtained results are presented in the form of percentages (P) and limits of 95% confidence interval (95% CI). Statistical significance of the difference between the indicators was determined using Pearson's χ^2 criterion (with Yates correction). The significance of differences between groups was established at $p < 0.05$.

RESULTS

65.1% of children had a body weight corresponding to their height, which was classified as HPD and was recorded more frequently in girls (67.5[66.4–68.6]%) than in boys (63.1[62.0-64.2]%; p=0.007; χ^2=7.2). Disharmonious variants of physical development due

Table 1. Results of running at a distance of 30 meters (%[95%CI])

Таблица 1. Результаты бега на дистанцию 30 метров (%[95%ДИ])

Пол / Sex	Нутритивный статус / Nutritional status	Показатели ГТО / GTO indicators			
		«золото» / “gold”	«серебро» / “silver”	«бронза» / “bronze”	«незачет» / “failure”
Мальчики / Boys n=1727	1. НП / M n=62	79,6 [74,2–85,0]	3,7 [1,2–6,1]	7,4 [3,9–10,8]	9,3 [5,4–13,2]
	2. ПП / RN n=132	81,0 [77,4–84,6]	2,5 [1,1–3,9]	5,8 [3,7–7,9]	10,7 [7,9–13,5]
	3. ГФР / HPD n=1089	80,2 [79,1–81,4]	2,9 [2,5–3,3]	7,6 [6,8–8,4]	9,3 [8,4–10,2]
	4. ИзМТ / Ov n=191	79,5 [76,4–82,3]	3,5 [2,1–4,9]	5,8 [4,1–7,6]	11,2 [8,8–13,6]
	5. Ож / Ob n=253	73,0 [70,1–75,9]	4,3 [3,1–5,6]	10,9 [8,9–12,8]	11,8 [9,7–13,9]
Девочки / Girls n=1522	6. НП / M n=51	64,6 [57,7–71,5]	18,7 [13,1–24,3]	8,3 [4,4–12,2]	8,4 [4,4–12,3]
	7. ПП / RN n=111	78,4 [74,5–82,3]	8,8 [6,0–11,5]	4,9 [2,8–7,0]	7,9 [5,2–10,6]
	8. ГФР / HPD n=1028	82,1 [80,9–83,4]	6,3 [5,5–7,1]	5,6 [4,9–6,3]	6,0 [5,2–6,8]
	9. ИзМТ / Ov n=156	80,3 [77,1–83,5]	3,4 [1,9–4,8]	3,4 [1,9–4,8]	12,9 [10,2–15,7]
	10. Ож / Ob n=176	76,2 [73,0–79,4]	7,1 [5,1–8,9]	10,7 [8,3–13,1]	6,0 [4,2–7,8]
Примечание / Note		P_{6-8}=0,002 (χ^2=9,2) P_{6-9}=0,03 (χ^2=4,9)	P_{6-8}=0,001 (χ^2=10,9) P_{6-9}=0,0003 (χ^2=12,8) P_{6-10}=0,02 (χ^2=5,7) P_{1-6}=0,01 (χ^2=6,0) P_{2-7}=0,04 (χ^2=4,4) P_{3-8}=0,0002 (χ^2=13,5)	P_{9-10}=0,001 (χ^2=10,1)	P_{8-9}=0,002 (χ^2=9,7) P_{3-8}=0,004 (χ^2=8,2) P_{5-10}=0,05 (χ^2=3,8)

Примечание / Note: ГФР / HPD — гармоничное физическое развитие / harmonious physical development; ИзМТ / Ov — избыточная масса тела / overweight; НП / M — недостаточность питания / malnutrition; Ож / Ob — ожирение / obesity; ПП / RN — пониженное питание / reduced nutrition.

to underweight were less frequent (10.9%) than those associated with overweight (24.0%). Malnutrition was found in 3.6[3.2–4.0]% of boys and 3.3[2.9–3.7]% of girls; another 7.6[7.0–8.1]% of boys and 7.3[6.6–8.0]% of girls were underweight. Overweight was equally frequent in boys (11.1[10.4–11.8]%) and girls (10.2[9.4–11.0]%). BMI, which corresponds to diagnostic criteria for obesity, was recorded more frequently in boys (14.6[13.4–15.4]%) than in girls (11.7[10.9–12.5]%; p=0.009; χ^2=6.7), which corresponds to the results of other studies [25, 26].

We selected those tasks which preschoolers can prepare for and successfully perform in accordance with physiologists' estimation. Previous studies have shown that children in kindergartens can only fully complete the 30-metre running standard. Long jump from a place, shuttle run and throwing a tennis ball (sandbag) into a target are not fully available for preschoolers; unfortunately, children face significant difficulties in performing other tests of the complex [8, 12].

Most preschoolers showed good development of speed qualities. They coped with overcoming the distance of 30 m in time corresponding to the standards of the "gold" badge; the data are presented in Table 1. Obese boys received the "gold" badge less often than their peers with other nutritional status, but the difference is not statistically significant. Among girls, preschool girls with MN and Ob have worse results. However, only girls with MN have a statistical difference with their peers with HPD (0.002) and OW (0.03). Boys received the "silver" badge more often than girls, and children with MN, UN and HPD showed a statistically significant difference (p=0.04–0.0002). Among boys, there was no correlation between the frequency of receiving the "silver" badge and the level of nutritional status. Girls with MN more often fulfilled the standards of "silver" badge than those with HPD, OW and Ob (p=0.02–0.0003). The "bronze" badge was more often obtained by girls with Ob than by boys (p=0.001), other indicators were not statistically different. No difference was found for preschoolers who failed the test in boys; girls with Ob had a higher rate of failure than their peers with HPD (p=0.002). Gender differences were found in children with HPD and Ob (more boys; p=0.05–0.004).

Participants showed satisfactory speed and strength qualities when performing a jump from a place with a push using two legs; the data are presented in Table 2. Girls more often fulfilled the "gold" badge. Moreover, the difference between children with UN and HPD was statistically significant (p=0.02–0.0004). Boys with HPD and OW were more successful, the difference with the peers with Ob is statistically significant (p=0.0009–0.0000). Girls with Ob demonstrated the minimum number of "gold" results, the difference is statistically significant in all cases (p=0.04–0.0000) except for the subgroup of children with MN. In terms of "silver" badge depending on gender, statistically significant difference of indicators was found only in children with UW (boys prevailed, p=0.03). Ob group of boys received "silver" more often than children with other nutritional status. They statistically differed from their peers with HPD (p=0.0007) and OW (p=0.03). Girls with OW and Ob received the "silver" badge more often than peers with HPD (p=0.04-0.009), and preschoolers with MN obtained the "silver" badge more often than those with UN (p=0.02) and with other levels of nutritional status. "Bronze" badge was more often received by both boys and girls with Ob, but the difference of indicators is not statistically significant. Boys did not pass this test more frequently. HPD groups had a statistically significant difference (p=0.0000). In both gender groups there are no children with MN; and there are fewer children with HPD than with other nutritional status, but the statistical difference in indicators is noted only in girls.

The results of hitting the target with a tennis ball, which characterize the development of movement coordination in children, are shown in Table 3. Girls with all types of nutritional status coped better and received the "gold" badge, the difference is statistically significant (p=0.0008–0.0000), no significant differences were found within gender groups. The "silver" badge were more often registered in boys than in girls, the difference of indicators in children with UN, HPD and Ob is statistically significant.

"Bronze" badge among boys was more often received by OW children, but the difference of indicators is statistically significant only in comparison with peers with HPD (p=0.02). In girls, "bronze" badge was more often received by children with MN, statistically significant

Table 2. Children's jump results (%[95%CI])

Таблица 2. Результаты прыжка у детей (%[95%ДИ])

Пол / Sex	Нутритивный статус / Nutritional status	Показатели ГТО / GTO indicators			
		«золото» / "gold"	«серебро» / "silver"	«бронза» / "bronze"	«незачет» / "failure"
Мальчики / Boys n=1727	1. НП / M n=62	56,4 [50,2–62,6]	37,1 [31,0–43,2]	6,5 [3,4–9,6]	0
	2. ПП / RN n=132	53,8 [49,5–58,1]	33,3 [29,2–37,4]	5,3 [3,4–7,2]	7,6 [5,3–9,9]
	3. ГФР / HPD n=1089	60,5 [59,0–61,9]	30,0 [28,6–31,4]	4,9 [4,3–5,5]	4,6 [4,0–5,2]
	4. ИзМТ / Ov n=191	60,2 [57,8–62,6]	30,9 [27,6–34,2]	5,2 [6,9–11,3]	3,7 [2,3–5,1]
	5. Ож / Ob n=253	44,3 [41,2–47,4]	41,1 [38,0–18,5]	7,1 [5,5–8,7]	7,5 [5,9–9,1]
Девочки / Girls n=1522	6. НП / M n=51	58,8 [51,9–65,7]	37,2 [30,5–43,9]	4,0 [3,4–4,6]	0
	7. ПП / RN n=111	68,5 [64,1–72,9]	20,7 [16,9–24,5]	5,4 [3,3–7,5]	5,4 [3,3–7,5]
	8. ГФР / HPD n=1028	67,9 [66,5–69,3]	26,7 [25,8–27,6]	4,0 [3,4–4,6]	1,4 [1,0–1,8]
	9. ИзМТ / Ov n=156	59,6 [55,7–63,5]	34,6 [30,8–38,4]	3,8 [2,3–5,3]	2,0 [0,9–3,1]
	10. Ож / Ob n=176	48,3 [44,6–52,4]	36,4 [32,8–40,0]	9,1 [7,0–11,2]	6,2 [4,4–8,0]
Примечание / Note		P_{3-5} =0,0000 (χ^2=22,3) P_{4-5} =0,0009 (χ^2=11,1) P_{7-10}=0,0008 (χ^2=11,2) P_{8-10}=0,0000 (χ^2=25,4) P_{9-10}=0,04 (χ^2=4,3) P_{8-9}=0,04 (χ^2=4,2) P_{2-7}=0,02 (χ^2=5,4) P_{3-8}=0,0004 (χ^2=12,5)	P_{3-5}=0,0007 (χ^2=11,7) P_{4-5}=0,03 (χ^2=4,9) P_{6-7}=0,02 (χ^2=5,0) P_{8-10}=0,009 (χ^2=6,9) P_{8-9}=0,04 (χ^2=4,2) P_{2-7}=0,03 (χ^2=4,8)	–	P_{7-8}=0,002 (χ^2=9,5) P_{8-10}=0,0000 (χ^2=17,6) P_{3-8}=0,0000 (χ^2=18,0)

Примечание / Note: ГФР / HPD — гармоничное физическое развитие / harmonious physical development; ИзМТ / Ov — избыточная масса тела / overweight; НП / M — недостаточность питания / malnutrition; Ож / Ob — ожирение / obesity; ПП / RN — пониженное питание / reduced nutrition.

level of indicators with peers with HPD was confirmed. Gender differences of indicators were revealed in children with HPD and Ob (boys more often fulfilled the "bronze" standard). Boys failed the test more often than girls. Statistical significance of differences was found in children with MN, HPD and Ob (p=0.02–0.0000). No statistically significant difference of indicators was found within gender groups.

The most difficult test for preschoolers in our study was shuttle run, which allows us to assess simultaneously the degree of development of speed qualities and coordination of movements, the results are shown in Table 4. Girls coped better and won the "golden" badge more often than boys. Excluding children with MN, the difference is statistically significant (p=0.03–0.0000). As for the gender groups, boys with

Table 3. Children's ball throwing results (%[95%CI])

Таблица 3. Результаты броска мяча у детей (%[95%ДИ])

Пол / Sex	Нутритивный статус / Nutritional status	Показатели ГТО / GTO indicators			
		«золото» / "gold"	«серебро» / "silver"	«бронза» / "bronze"	«незачет» / "failure"
Мальчики / Boys n=1727	1. НП / M n=62	38,5 [32,3–44,7]	23,1 [17,9–28,3]	18,5 [13,7–23,3]	19,9 [15,0–24,8]
	2. ПП / RN n=132	36,9 [32,7–41,1]	28,5 [24,6–32,4]	16,1 [12,9–19,3]	18,5 [15,1–21,9]
	3. ГФР / HPD n=1089	43,7 [42,2–45,1]	26,6 [25,4–27,8]	15,8 [14,7–16,9]	13,9 [12,8–14,7]
	4. ИзМТ / Ov n=191	38,4 [34,9–41,8]	27,4 [24,3–30,2]	22,6 [19,5–25,4]	11,6 [9,3–13,9]
	5. Ож / Ob n=253	39,9 [36,8–43,0]	28,6 [25,7–31,5]	18,1 [15,7–20,5]	13,4 [11,2–15,6]
Девочки / Girls n=1522	6. НП / M n=51	70,0 [63,5–76,4]	12,0 [7,4–16,6]	12,0 [7,4–16,6]	6,0 [2,7–9,3]
	7. ПП / RN n=111	58,1 [53,3–62,9]	17,1 [13,5–20,7]	20,0 [19,1–20,9]	4,8 [2,7–6,9]
	8.ГФР / HPD n=1028	63,2 [61,9–64,5]	17,3 [16,1–18,5]	12,6 [11,7–13,6]	6,9 [6,1–7,7]
	9.ИзМТ / Ov n=156	59,7 [55,8–63,6]	19,5 [16,3–22,7]	14,3 [11,5–17,1]	6,5 [4,4–8,3]
	10.Ож / Ob n=176	61,2 [57,5–64,9]	19,1 [16,2–22,0]	13,3 [10,7–15,9]	6,4 [4,6–8,2]
Примечание / Note		P_{1-6}=0,0008 (χ^2=11,3) P_{2-7}=0,001 (χ^2=10,5) P_{3-8}=0,0000 (χ^2=79,3) P_{4-9} =0,0000 (χ^2=15,5) P_{5-10}=0,0000 (χ^2=18,6)	P_{2-7}=0,04 (χ^2=4,1) P_{3-8}=0,0000 (χ^2=25,8) P_{5-10}=0,02 (χ^2=5,0)	P_{3-4}=0,02 (χ^2=5,3) P_{7-8}=0,03 (χ^2=4,5) P_{3-8}=0,03 (χ^2=4,4) P_{4-9}=0,05 (χ^2=3,9)	P2-7=0,001 (χ2=10,1) P3-8=0,0000 (χ2=27,4) P5-10=0,02 (χ2=5,2)

Примечание / Note: ГФР / HPD — гармоничное физическое развитие / harmonious physical development; ИзМТ / Ov — избыточная масса тела / overweight; НП / M — недостаточность питания / malnutrition; Ож / Ob — ожирение / obesity; ПП / RN — пониженное питание / reduced nutrition.

Ob performed worse. They had statistically significantly lower results than their peers with HPD and MN. Girls with Ob and MN performed worse. Boys more often than girls received "silver" badges, the performance was statistically significantly different among children with HPD, OW and Ob (p=0.007–0.0000), no statistically significant difference was found within gender groups. Boys showed results corresponding to "bronze" more often than girls, but the difference of indicators is not statistically significant. More "bronze" badges were obtained by boys with MN, their indicators were statistically higher than those of their peers with HPD, OW and Ob (p=0.02–0.005). In girls, children with MN also more often fulfilled the "bronze" standard; the difference is statistically significant when compared to their peers with HPD and OW. More than 1/3 of participants failed the test. Boys with MN and HPD were less likely to fail. Girls were less likely to fail if they had UN or HPD. The difference of statistical significance between boys and girls was found only in the group of children with MN (p=0.05).

Table 4. Shuttle run results (%[95%CI])

Таблица 4. Результаты челночного бега (%[95%ДИ])

Пол / Sex	Нутритивный статус / Nutritional status	Показатели ГТО / GTO indicators			
		«золото» / “gold”	«серебро» / “silver”	«бронза» / “bronze”	«незачет» / “failure”
Мальчики / Boys n=1727	1. НП / M n=62	28,3 [22,2–34,4]	20,7 [15,2–26,1]	7,5 [3,9–11,1]	43,5 [36,7–50,3]
	2. ПП / RN n=132	32,8 [28,5–37,1]	22,7 [18,9–26,5]	18,5 [15,0–21,9]	26,0 [22,1–29,9]
	3. ГФР / HPD n=1089	32,6 [31,1–34,0]	23,4 [22,1–24,7]	10,0 [9,1–10,9]	34,0 [32,5–35,4]
	4. ИзМТ / Ov n=191	26,1 [22,6–29,5]	23,0 [19,7–26,3]	9,1 [6,9–11,3]	41,8 [38,0–45,6]
	5. Ож / Ob n=253	20,5 [17,8–23,2]	28,8 [25,9–31,8]	8,2 [6,4–9,9]	42,5 [39,2–45,8]
Девочки / girls n=1522	6. НП / M n=51	49,0 [42,1–55,9]	13,7 [8,9–18,5]	5,9 [2,6–9,2]	31,4 [24,9–37,8]
	7. ПП / RN n=111	40,5 [35,9–45,1]	13,5 [10,3–16,7]	8,1 [5,5–10,7]	37,9 [33,3–42,5]
	8. ГФР / HPD n=1028	51,7 [50,2–53,2]	12,7 [11,7–13,6]	4,0 [3,4–4,6]	31,6 [30,2–33,0]
	9. ИзМТ / Ov n=156	48,1 [44,1–52,0]	11,5 [9,0–14,1]	2,6 [1,3–3,9]	37,8 [33,9–41,7]
	10. Ож / Ob n=176	44,1 [40,4–47,8]	13,5 [10,9–16,1]	3,9 [2,4–5,4]	38,5 [34,9–42,1]
Примечание / Note		P_{2-5}=0,01 (χ^2=6,2) P_{3-5}=0,0004 (χ^2=12,3) P_{8-10}=0,05 (χ^2=3,8) P_{1-6}=0,03 (χ^2=7,7) P_{3-8}=0,0000 (χ^2=74,9) P_{4-9}=0,0000 (χ^2=16,7) P_{5-10}=0,0000 (χ^2=25,3)	P_{3-8}=0,0000 (χ^2=39,2) P_{4-9}=0,007 (χ^2=7,3) P_{5-10}=0,0003 (χ^2=13,2)	P_{2-5} =0,005 (χ^2=7,8) P_{2-3} =0,005 (χ^2=7,9) P_{2-4} =0,02 (χ^2=5,4) P_{7-8} =0,04 (χ^2=4,1) P_{7-9} =0,04 (χ^2=4,3)	P_{1-2} =0,02 (χ^2=5,1) P_{2-4} =0,006 (χ^2=7,5) P_{2-5} =0,003 (χ^2=8,9) P_{2-7}=0,05 (χ^2=3,7)

Примечание / Note: ГФР / HPD — гармоничное физическое развитие / harmonious physical development; ИзМТ / Ov — избыточная масса тела / overweight; НП / M — недостаточность питания / malnutrition; Ож / Ob – ожирение / obesity; ПП / RN — пониженное питание / reduced nutrition.

CONCLUSION

Physical performance of children and adolescents can be determined in most cases by assessing speed, strength, agility, flexibility, endurance and velocity-force qualities by means of control exercises — tests. In our country, the All-Russian physical culture and sports complex “Ready for Labor and Defense” has been developed, which allows to unify the assessment of physical training and ensure the continuity of physical education in schools [27]. The most widely used analogues of the “GTO” abroad are the European Physical Fitness Test (EUROFIT) and the California Physical Fitness Assessment Test

[28]. The GTO complex, as well as the EUROFIT test, is proposed to assess motor skills of children from 6 y.o. However, according to physiologists, preschool children are not mature enough to perform a number of tests of the first stage of the "GTO" (for the age group from 6 to 8 years), which reduces the test results [8, 12, 29]. It might be explained by the period of intensive physical ("half-growth" spurt) and active mental development.

Taking into account this circumstance, we used only 4 tests that allowed us to assess the level of development of speed, speed-force and coordination qualities of physical development. The level of children's physical development appeared to be ambiguous. Girls coped with all tests better than boys. Except for throwing a tennis ball into the target, there was no difference in the results of the test depending on nutritional status. In all other tests, children with a harmonious ratio of height to body weight were more successful, more often showing the standard of the "gold" badge. Peers with disharmonious variants of physical development (especially with obesity and malnutrition) coped with the task less often and their results were lower than the scores. Our results correlate with the data of other authors [27, 29–32].

Summarizing the above, it is possible to conclude that physical qualities of the participants are irregularly developed and have a great variability depending on gender and nutritional status, which stipulates the need for a differentiated approach when conducting physical training sessions and admission to participation in the "GTO" tests.

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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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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EVALUATION OF TEMPOROMANDIBULAR JOINT CONDITION AFTER HARDWARE-SURGICAL TREATMENT OF DENTO-MANDIBULAR ANOMALIES IN YOUNG PATIENTS

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ABSTRACT. ***Introduction.*** Nowadays there is an increased attention to facial aesthetics. More and more often dento-mandibular anomalies, in which temporomandibular joint (TMJ) is affected, are treated by hardware-surgical method. At the same time, when eliminating dento-mandibular anomalies, the condition of the temporomandibular joint is often not evaluated in the long term. ***The purpose of the study*** was to assess the condition of the temporomandibular joint after orthodontic treatment and orthognathic operations in young people. ***Materials and methods.*** In this work we have carried out a clinical evaluation of the temporomandibular joint in 13 young people suffering from lower macrognathia after orthodontic treatment and orthognathic surgeries. ***Result.*** It was found that all the patients suffering from inferior macrognathia who took part in the study had pathological symptoms of the temporomandibular joint characteristic of its painful dysfunction before the complex hardware-surgical treatment. The orthodontic treatment performed in the patients practically did not change the clinical symptoms of the temporomandibular joint. Both before the orthodontic stage and after its completion, pathologic symptoms of the temporomandibular joint persisted. In the distant period after the completion of the surgical stage of treatment, the reliable effectiveness of complex therapy with regard to the TMJ condition was noted, which amounted to 10.64%. However, it should be taken into account that pathologic symptoms of the temporomandibular joint after the completion of hardware-surgical treatment remained in all the examined patients, despite the fact that in some of them their severity slightly decreased. In one patient, despite the good aesthetic effect of complex hardware-surgical therapy, the condition of the temporomandibular joint worsened from mild to moderate severity of pain dysfunction. ***Conclusion.*** Timely informing patients about the expected effectiveness of treatment and possible complications within the framework of the patient's signing an informed consent for treatment or intervention is an important factor of conflict prevention in dentistry and maxillofacial surgery.

KEYWORDS: *young people, dento-mandibular anomalies, temporomandibular joint, temporomandibular joint pain dysfunction, inferior macrognathia, hardware-surgical treatment, orthodontic treatment, orthognathic surgeries*

ОЦЕНКА СОСТОЯНИЯ ВИСОЧНО-НИЖНЕЧЕЛЮСТНОГО СУСТАВА ПОСЛЕ АППАРАТУРНО-ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЗУБОЧЕЛЮСТНЫХ АНОМАЛИЙ У МОЛОДЫХ ЛЮДЕЙ

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РЕЗЮМЕ. ***Введение.*** В настоящее время существует повышенное внимание к эстетике лица. Все чаще зубочелюстные аномалии, при которых страдает височно-нижнечелюстной сустав, лечат аппаратурно-хирургическим способом. В то же время при устранении зубочелюстных аномалий часто не оценивается в отдаленном периоде состояние височно-нижнечелюстного сустава (ВНЧС). ***Цель исследования*** — оценка состояния височно-нижнечелюстного сустава после ортодонтического лечения и ортогнатических операций у молодых людей. ***Материалы и методы.*** В работе проведена клиническая оценка состояния ВГЧС у 13 молодых людей, страдающих нижней макрогнатией, после ортодонтического лечения и ортогнатических операций. ***Результаты.*** Установлено, что все принявшие участие в исследовании пациенты, страдавшие нижней макрогнатией, имели до начала комплексного аппаратурно-хирургического лечения патологические симптомы со стороны ВНЧС, характерные для его болевой дисфункции. Проведенное ортодонтическое лечение у пациентов практически не изменило клинической картины со стороны ВНЧС. Как до ортодонтического этапа, так и по его завершению патологические симптомы со стороны ВНЧС сохранялись. В отдаленном периоде после завершения хирургического этапа лечения отмечена достоверная эффективность комплексной терапии в отношении состояния ВНЧС, которая составила 10,64%. Однако следует учитывать, что патологические симптомы со стороны ВНЧС после завершения аппаратурно-хирургического лечения сохранились у всех обследованных пациентов, несмотря на то что у некоторых больных их выраженность несколько уменьшилась. У одного пациента, несмотря на хороший эстетический эффект комплексной аппаратурно-хирургической терапии, состояние со стороны ВНЧС ухудшилось с легкой степени тяжести болевой дисфункции до средней тяжести. ***Заключение.*** Своевременное информирование пациентов о предполагаемой эффективности лечения и возможных осложнениях в рамках подписания пациентом информированного согласия на лечение или вмешательство является важным фактором профилактики конфликтов в стоматологии и челюстно-лицевой хирургии.

КЛЮЧЕВЫЕ СЛОВА: *люди молодого возраста, зубочелюстные аномалии, височно-нижнечелюстной сустав, болевая дисфункция височно-нижнечелюстного сустава, нижняя макрогнатия, аппаратурно-хирургическое лечение, ортодонтическое лечение, ортогнатические операции*

INTRODUCTION

There is an increased attention to facial aesthetics nowadays. Dento-mandibular anomalies (DMA) and facial asymmetries are treated not only by orthodontic methods, but also by orthognathic surgeries [1, 2]. In this case, the position of the mandibular heads in relation to the temporal bone articular fossae is often changed. In other words, certain changes in the spatial position of the temporomandibular joint (TMJ) elements occur [3]. At the same time, temporomandibular arthralgia often occurs during orthodontic treatment or soon after it. Temporomandibular arthralgia is distressing for patients, is poorly treatable and is often causes complaints, claims and lawsuits against medical organizations by patients who believe that they have been treated incorrectly [4, 5]. It is believed that the elimination of DMA and facial asymmetries will have a positive effect on the functional status of the TMJ [6, 7]. However, no research has been conducted.

AIM

The aim of the study was to evaluate the condition of the temporomandibular joint after orthodontic treatment and orthognathic surgeries in young adults.

MATERIALS AND METHODS

The research included 13 males aged 22 to 28 years who suffered from lower macrognathia and underwent consecutive orthodontic treatment with bracket systems and surgical treatment with orthognathic interventions. The patients underwent bilateral oblique sliding osteotomy of the mandible as orthognathic surgery. All patients were clinically evaluated for TMJ condition before the complex treatment had been started, after the active stage of orthodontic treatment, and 12–18 months after surgical treatment according to the previously proposed methodology. It involves assessment of the state of mouth opening, the presence of mandibular deviation when opening and closing the mouth, the presence of sound phenomena in the TMJ area during mandibular movement, as well as the presence of joint pain in the state of physiological rest of the mandible and during its movement [8]. Based on these parameters, the severity of TMJ pathology was determined, as well as the effectiveness of treatment during the specified periods of patient follow-up.

The study complies with ethical standards of the Committee on Human Experiments of the Helsinki Declaration issued in 1975 and revised in 2000.

The digital material obtained was processed on a personal computer using a specialized statistical analysis package Statistica for Windows v. 6.0. Differences between the compared groups were considered reliable at $p \leq 0.05$. Instances with p-value in the range from 0.05 to 0.10 were regarded as a tendency.

RESULTS AND DISCUSSION

Clinical study revealed that 11 (84.62%) out of 13 young patients suffering from inferior macrognathia had TMJ pathology in the form of mild TMJ pain dysfunction (ICD-10 code — K07.60), and 2 (15.38%) patients were diagnosed with similar pathology of moderate severity. The examined patients were most often diagnosed with symptoms associated with sounds (crepitation, crunching, clicking), as well as deviation of the lower jaw when opening and closing the mouth from 2 to 5 mm, less often it was determined by limitation of mouth opening. Orthodontic treatment with vestibular bracket systems lasted from 11 to 15 months. After its completion, the TMJ condition was also evaluated. Although the clinical condition in this group of patients improved, the effectiveness of treatment at this stage was extremely low and amounted to 2.13% ($p > 0.05$). However, there were no changes in terms of the severity among the examined patients. Mild degree of TMJ pathology was revealed in 11 patients, and 2 patients had moderate pathology ($p > 0,05$). A positive dynamics was associated with a decrease in pathological symptoms of TMJ (Fig. 1, 2).

Orthognathic surgeries successfully performed on all patients changed patients' appearance, improved their mental state and internal picture of the disease. At the same time, speaking about the TMJ condition, it is necessary to emphasize that 1 (7.69%) patient,

who suffered from a mild degree of severity of TMJ pathology before the complex treatment, had a worsening to a medium degree of severity of the disease, namely painful TMJ dysfunction. 2 (15.38%) patients with moderate TMJ pathology showed improvement of their condition and changed it over to a mild degree. However, pathological symptoms of TMJ did not disappear at all, similarly to all the examined patients (Fig. 1). Although effectiveness of the treatment was reliable ($p < 0.05$) in terms of the intensity of the clinical picture in the remote period after the surgical stage of treatment ($p < 0.05$) and amounted to 10.64% (Fig. 2).

Thus, it should be noted that, despite the comprehensive hardware and surgical treatment of inferior macrognathia, the pathological symptoms persisted, although in some cases their intensity was slightly reduced, as evidenced by the obtained treatment efficacy indicators. One patient showed a worsened TMJ condition one year after the complex treatment was completed, as he was diagnosed with a mild degree of severity of TMJ pathology before the treatment and after the orthodontic stage. Unfortunately, the remote period demonstrated that the TMJ pathology switched to medium severity. This data should be taken into account when planning hardware and surgical treatment, especially when drawing up the patient's informed consent for orthodontic treatment and subsequent orthognathic care. Competent and timely awareness of a patient about possible results of treatment and its effectiveness, as well as complications, can reduce the number of complaints, claims and lawsuits in relation to complex treatment of DMA. It can also prevent forensic conclusions

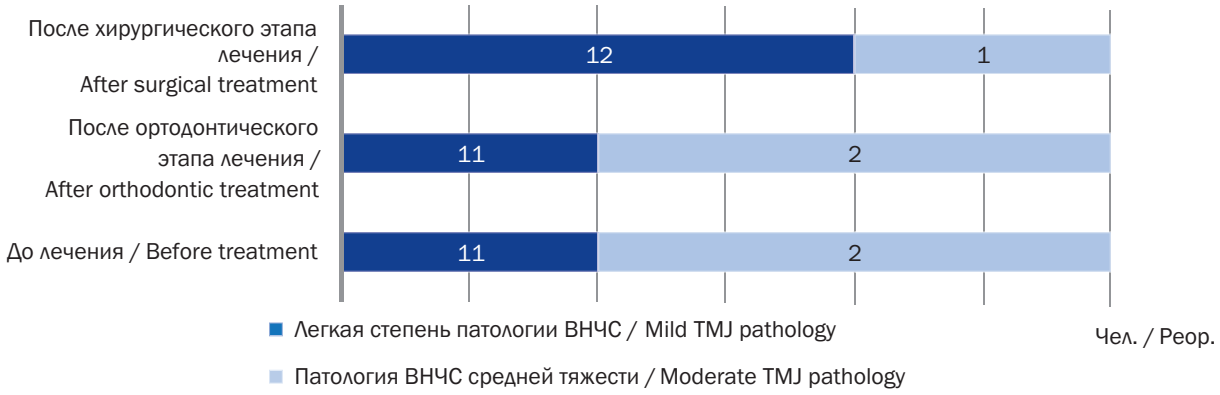

Fig. 1. Characteristics of the severity of temporomandibular joint (TMJ) pathology in the examined patients at the stages of complex treatment, people

Рис. 1. Характеристика степени тяжести течения патологии височно-нижнечелюстного сустава (ВНЧС) у обследуемых пациентов на этапах комплексного лечения, человек

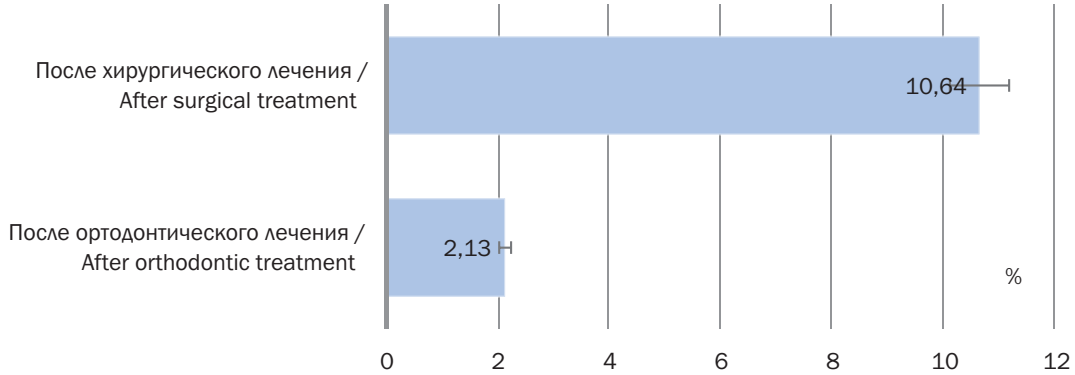

Fig. 2. The effectiveness of treatment of the examined patients after the stages of hardware-surgical treatment, %

Рис. 2. Эффективность лечения обследованных пациентов после этапов аппаратурно-хирургического лечения, %

about causal relationship between treatment and complications.

CONCLUSION

The conducted clinical research has shown that all the patients who took part in the study, suffering from TMJ, had pathological symptoms of TMJ before the complex appliance-surgical treatment. The orthodontic treatment performed in the patients practically did not change the clinical picture of TMJ. Pathological TMJ symptoms persisted both before the orthodontic stage and after its completion. Reliable effectiveness of TMJ complex therapy was noted in the remote period after the completion of the surgical stage of treatment, which amounted to 10.64%. However, it should be taken into account that TMJ pathological symptoms remained in all examined patients even after the hardware-surgical treatment had been completed, despite the fact that some patients noted that the severity slightly decreased. In addition, one patient showed a worsening of TMJ condition from mild to moderate TMJ pain dysfunction despite the good esthetic effect of complex orthodontic and surgical therapy. This indicates possible adverse effects of complex orthodontic and surgical treatment of TMJ, which take place in everyday practice and may become a reason for patients' claims to medical organizations. Timely informing patients about the expected effectiveness of treatment and possible complications as part of the patient's signing an informed consent for treatment or intervention is an important factor in conflict prevention in dentistry and maxillary and facial surgery.

ADDITIONAL INFORMATION

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DENTAL CARIES IN ADOLESCENTS WITH CEREBRAL PALSY

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ABSTRACT. ***Introduction.*** In cerebral palsy, spasticity of the chewing muscles is noted, which, against the background of motor disorders, adversely affects the features of the dental health of patients. ***The purpose of the study*** was to assess the incidence of dental caries and the intensity of its course in adolescents living in St. Petersburg and suffering from cerebral palsy. ***Materials and methods.*** To achieve the purpose of the study, 31 adolescents (22 boys and 9 girls) aged 14 to 17 years old living in St. Petersburg and suffering from cerebral palsy were examined. These patients made up 1 main group. For control, 75 adolescents (36 boys and 39 girls) aged 14 to 17 years old who did not suffer from any psychosomatic diseases were examined (control group 2). ***Result.*** It was found that, compared with their peers, adolescents living in In St. Petersburg and those suffering from cerebral palsy, against the background of unsatisfactory individual dental and oral care, there is a high incidence of dental caries (100%), which occurs in a decompensated form. All adolescents suffering from cerebral palsy needed dental rehabilitation measures. The low values of the index of the level of dental care (23.0%) also indicated an insufficient level of dental care among adolescents suffering from cerebral palsy. At the same time, dental caries in 13.33% of their peers did not occur at all. All adolescents in the control group performed well in individual oral care, and the level of dental care provided to them was good, which is also confirmed by indicators of the intensity of the carious process. ***Conclusion.*** Given the motor disorders that adolescents with cerebral palsy have, as well as the difficulties of oral care and dental treatment, they need special attention from dentists, who must teach parents, and then children themselves, the rules of dental and oral care, and also recommend them the most effective dental and oral care products, taking into account the low content of fluoride ion in drinking water in St. Petersburg.

KEYWORDS: *adolescents, cerebral palsy, dental caries, incidence of dental caries, intensity of dental caries, oral hygiene, level of dental care*

КАРИЕС ЗУБОВ У ПОДРОСТКОВ, СТРАДАЮЩИХ ДЕТСКИМ ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ

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РЕЗЮМЕ. ***Введение.*** При детском церебральном параличе (ДЦП) отмечается спастичность жевательной мускулатуры, что на фоне двигательных нарушений неблагоприятно отражается на особенностях стоматологического здоровья пациентов. ***Цель исследования*** — оценить встречаемость кариеса зубов и интенсивность его течения у подростков, проживающих в г. Санкт-Петербурге и страдающих детским церебральным параличом. ***Материалы и методы.*** Для реализации цели исследования были осмотрены 31 подросток (22 мальчика и 9 девочек) в возрасте от 14 до 17 лет, проживающих в г. Санкт-Петербурге и страдающих ДЦП. Эти пациенты составили 1-ю (основную) группу. Для контроля были обследованы 75 подростков (36 юношей и 39 девушек) в возрасте от 14 до 17 лет, которые не страдали какими-либо психосоматическими заболеваниями (2-я группа, контрольная). ***Результаты.*** Было установлено, что по сравнению со сверстниками, у подростков, проживающих в г. Санкт-Петербурге и страдающих ДЦП, на фоне неудовлетворительного индивидуального ухода за зубами и полостью рта отмечается высокая встречаемость кариеса зубов (100%), который протекает в декомпенсированной форме. Все подростки, страдающие ДЦП, нуждались в проведении стоматологических санационных мероприятий. Низкие значения показателя индекса уровня стоматологической помощи (23,0%) также свидетельствовали о недостаточном уровне стоматологической помощи среди подростков, страдающих ДЦП. В то же время у их сверстников кариес зубов в 13,33% случаев вообще не встречался. Все подростки, входившие в контрольную группу, хорошо выполняли мероприятия по индивидуальному уходу за полостью рта, а уровень стоматологической помощи, которая оказывалась им, был хороший, что также подтверждают показатели интенсивности течения кариозного процесса. ***Заключение.*** Учитывая имеющиеся у подростков, страдающих ДЦП, двигательные расстройства, а также сложности ухода за полостью рта и стоматологического лечения, они нуждаются в особом внимании со стороны врачей-стоматологов, которые должны с детского возраста обучать родителей, а потом и самих детей правилам ухода за зубами и полостью рта, а также рекомендовать им наиболее эффективные средства ухода за зубами и полостью рта, с учетом низкого содержания фторид-иона в питьевой воде г. Санкт-Петербурга.

КЛЮЧЕВЫЕ СЛОВА: *подростки, детский церебральный паралич, кариес зубов, встречаемости кариеса зубов, интенсивность течения кариеса зубов, гигиена полости рта, уровень стоматологической помощи*

INTRODUCTION

Child cerebral palsy (ICD-10 — G80) is characterized by spasticity of the masticatory muscles, which adversely affects the dental health of patients against the background of motor disorders [1]. It is especially important to provide patients suffering from cerebral palsy (CP) with good oral hygiene from childhood, which will help to preserve their dental health in later life. At the same time, a high prevalence of dental caries in children, adolescents and adults in St. Petersburg is known [2], which is promoted by insufficient fluoride ion content in drinking water [3–5]. However, the organization of dental sanitation measures for primary and secondary prevention of dental caries has significantly improved dental health in residents of St. Petersburg [6]. At present, there is no unified protocol for the management of children with cerebral palsy at dental appointments, so any measures that can increase the resistance of teeth to dental caries in children, adolescents, and adults are an urgent task of domestic practical medicine [7]. For this reason, the problem of providing dental care to patients with cerebral palsy is relevant.

AIM

To evaluate the occurrence of dental caries and the intensity of its course in adolescents suffering from cerebral palsy, living in St. Petersburg.

MATERIALS AND METHODS

31 adolescents (22 boys and 9 girls) aged 14 to 17 years were examined. All the participants lived in St. Petersburg and suffered from cerebral palsy. These patients constituted the 1st (main) group. 75 adolescents (36 boys and 39 girls) aged 14 to 17 years who did not suffer from any psychosomatic diseases were examined as controls (group 2, control group). Dental caries prevalence was assessed, which was expressed as a percentage. In addition, the intensity of dental caries was determined by the CFE index, which represents the sum of carious, filled, and extracted permanent teeth. The oral hygiene index was determined in all examined adolescents according to the method of Y.A. Fedorov and V.V. Volodkina [8]. The index of dental care level (DCL) was calculated according to the method of P.A. Leus [9].

The obtained digital material was processed by means of mathematical statistics methods. The achieved level of significance (p) was considered in all statistical analysis procedures; the critical level of significance was equal to 0.05. Cases where the probability values of the p-value ranged from 0.05 to 0.10 were considered as a tendency.

The research conformed to the ethical standards of the Committee on Human Experiments of the Helsinki Declaration on Human Experiments issued in 1975 and revised in 2000.

RESULTS

Dental examination of adolescents suffering from cerebral palsy revealed that all participants (100%) suffered from dental caries (Fig. 1). Moreover, the carious process was decompensated (Fig. 2), as the CFE index was 6.13 units (C=2.18; F=2.18; E=1.17). Obviously, the high prevalence of caries and the intensity of its course were attributed to poor dental care, as the oral hygiene index score of adolescents suffering from cerebral palsy was 2.34±0.19 units, which characterized their individual hygiene as poor (Fig. 3). The DCL index in adolescents with cerebral palsy was 23.0%. According to interpretations of this index, it shows an insufficient level of dental care for adolescents with cerebral palsy (Fig. 1).

As for the controls, the incidence of dental caries was 86.67%, as dental caries was not diagnosed in 10 adolescents (Fig. 1). The caries process in controls was compensated (Fig. 2) with a CFE index amounting to 3.44 units (K=0.15; P=3.17; U=0.12) against the background of good oral hygiene, as their hygiene index amounted to 1.37±0.21 units (Fig. 3). The control group of adolescents also showed a good level of dental care with a DCL index=92.15% (Fig. 1).

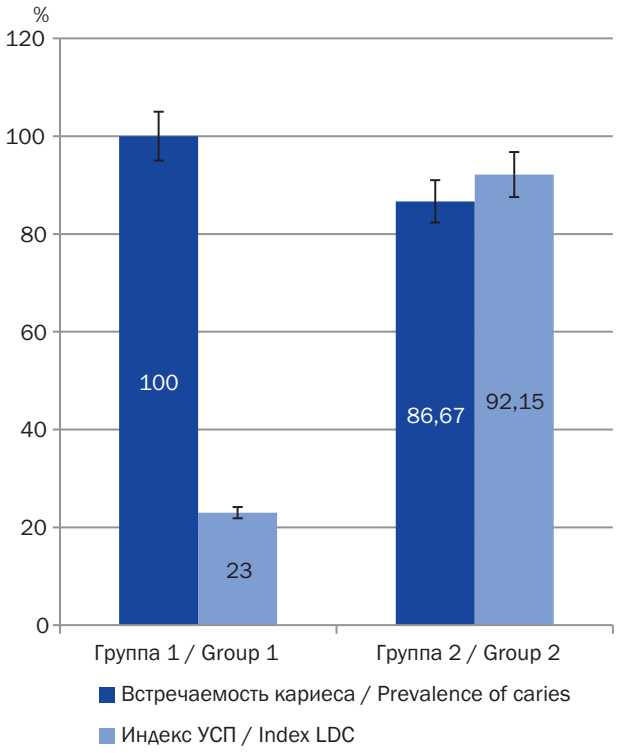

Fig. 1. Indicators of the occurrence of dental caries and the index of the level of dental care (LDC) in adolescents of the studied groups, %

Рис. 1. Показатели встречаемости кариеса зубов и индекса уровня стоматологической помощи (УСА) у подростков исследуемых групп, %

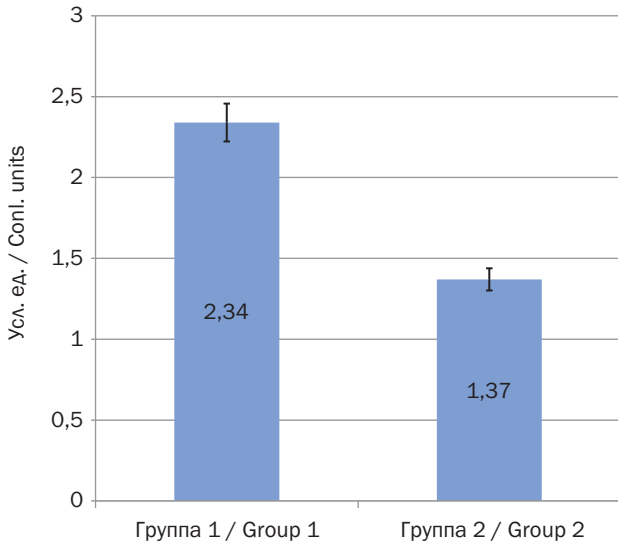

Fig. 3. Indicators of individual oral hygiene according to the Yu.A. Fedorov, V.V. Volodkina index in adolescents of the studied groups, conl. units

Рис. 3. Показатели индивидуальной гигиены полости рта по индексу Ю.А. Федорова, В.В. Володкиной у подростков исследуемых групп, усл. ед.

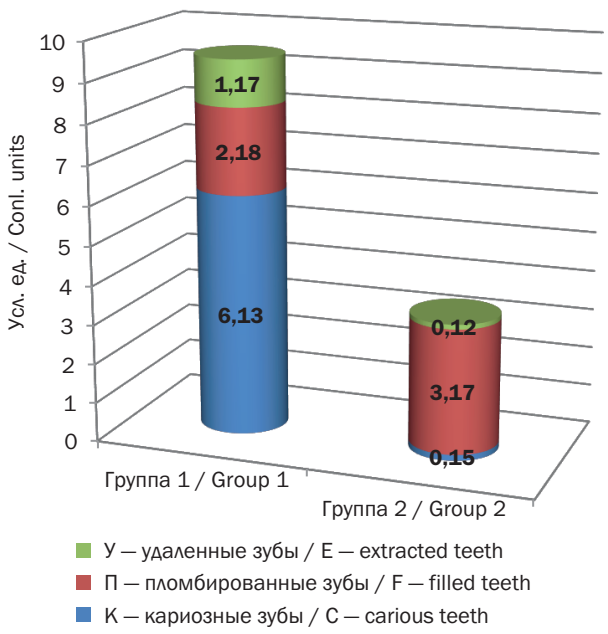

Fig. 2. Characteristics of the intensity of the course of the carious process according to the CFE index in adolescents of the studied groups, conl. units

Рис. 2. Характеристика интенсивности течения кариозного процесса по индексу КПУ у подростков исследуемых групп, усл. ед.

DISCUSSION

The research has revealed that adolescents living in St. Petersburg and suffering from cerebral palsy have a high incidence of dental caries (100%), which is decompensated, in comparison with their peers against the background of unsatisfactory individual care of teeth and oral cavity. At the same time, all adolescents suffering from cerebral palsy needed treatment or extraction of teeth, i.e. dental sanitation measures. Low values of the CFE index also indicate an insufficient level of dental care among adolescents suffering from cerebral palsy. At the same time, 13.33% (10 individuals) had no dental caries at all. All the adolescents in the control group performed well in their individual oral care activities and the level of dental care they received was good, which is also confirmed by the caries intensity indicators.

CONCLUSION

Summarizing the above, we can conclude that adolescents suffering from cerebral palsy, owing to

their movement disorders, difficulties in oral care and dental treatment due to spasticity of the masticatory muscles, need special attention from dentists. Dentists should teach parents from childhood and then children themselves the rules of dental and oral care, as well as recommend them the most effective means of dental and oral care, taking into account the low content of fluoride ion in drinking water in St. Petersburg. It is obvious that children and adolescents, as well as adult patients suffering from cerebral palsy, should be under the dynamic supervision of a dentist. Only such an approach will improve the dental health indicators of people suffering from cerebral palsy.

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.

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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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THE OUTCOMES OF TRUE PREMATURE SEXUAL DEVELOPMENT IN GIRLS AFTER COMPLETION OF CYCLIC SUPPRESSIVE THERAPY

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ABSTRACT. ***Introduction.*** In the practice of a pediatric endocrinologist, there is a well-developed algorithm of actions to assess the causes and decide on treatment options for a patient with true premature sexual development (iPPR). After eliminating the volumetric formation of the central nervous system, cyclic suppressive therapy with triptorelin is prescribed. ***The purpose*** of this study was to study the formation of puberty in girls after the end of iPPR therapy with triptorelin. To achieve this goal, tasks were set, including the analysis of medical records of girls with iPPR who had previously received triptorelin therapy; conducting an online questionnaire of patients on the formation of their puberty period with an assessment of growth, determining the time of menstruation after drug withdrawal; studying family history concerning the start of puberty in relatives. A literary search on the topic of the study revealed that in recent years information has appeared about the genetic basis of iPPR. ***The results*** of the study showed that the duration of cyclic suppressive therapy with triptorelin iPPR affects the timing of the appearance of the first menstruation in patients. With therapy for more than 5 years, menstruation occurs later than in patients using the drug for a shorter period of time. In most patients, an important goal of therapy was achieved — the prevention of accelerated bone differentiation with premature closure of growth zones and stunting. With delayed initiation of therapy, stunting could not be prevented. ***Conclusions.*** Clinical manifestations of sexual development in patients after completion of treatment with triptorelin prove the reversibility of its antigonadotropic effect. The formation of the menstrual cycle after discontinuation of treatment occurs later in those who have used the drug for more than 5 years. Timely initiation of iPPR treatment helps to avoid stunting in most patients. To verify the genesis of iPPR, it is advisable to conduct a molecular genetic study, given the high frequency of familial forms of this disease. It is important to know the long-term results of the use of suppressive therapy of iPPR, its possible impact on the reproductive period of patients' lives.

KEYWORDS: *true premature sexual development, outcomes of suppressive cyclic therapy with triptorelin, puberty formation, molecular genetic studies*

ИСХОДЫ ИСТИННОГО ПРЕЖДЕВРЕМЕННОГО ПОЛОВОГО РАЗВИТИЯ У ДЕВОЧЕК ПОСЛЕ ЗАВЕРШЕНИЯ ЦИКЛИЧЕСКОЙ СУПРЕССИВНОЙ ТЕРАПИИ

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РЕЗЮМЕ. ***Введение.*** В практике детского эндокринолога для оценки причин и принятия решения о вариантах лечения пациента с истинным преждевременным половым развитием (иППР) существует отработанный алгоритм действий. После исключения объемного образования центральной нервной системы назначают циклическую супрессивную терапию трипторелином. ***Целью*** данного исследования было изучение становления пубертатного периода у девочек после окончания терапии иППР трипторелином. Для достижения цели были поставлены задачи, включающие анализ медицинских карт девочек с иППР, ранее получавших терапию трипторелином; проведение онлайн-анкетирования пациенток по вопросам становления у них пубертатного периода с оценкой роста, определением времени появления менструации после отмены препарата, изучение семейного анамнеза, касающегося старта пубертата у родственников. Литературный поиск по теме исследования выявил, что в последние годы появилась информация о генетических основах иППР. ***Результаты*** проведенного исследования, показали, что длительность циклической супрессивной терапии трипторелином иППР влияет на сроки появления первой менструации у пациенток. При терапии более 5 лет менструации наступают позже, чем у пациенток, применяющих препарат более короткий период. У большинства пациенток была достигнута важная цель терапии — предупреждение ускоренной дифференцировки костей с преждевременным закрытием зон роста и низкорослостью. При отсроченном начале терапии предотвратить низкорослость не удалось. ***Выводы.*** Клинические проявления полового развития у пациенток после завершения лечения трипторелином доказывают обратимость его антигонадотропного действия. Становление менструального цикла после отмены лечения наступает позже у тех, кто применял препарат более 5 лет. Своевременное начало лечения иППР помогает избежать низкорослости у большинства пациенток. Для верификации генеза иППР целесообразно проведение молекулярно-генетического исследования, учитывая высокую частоту семейных форм этого заболевания. Важно знать долгосрочные результаты использования супрессивной терапии иППР, возможное ее влияние на репродуктивный период жизни пациенток.

КЛЮЧЕВЫЕ СЛОВА: *истинное преждевременное половое развитие, исходы супрессивной циклической терапии трипторелином, становление пубертатного периода, молекулярно-генетические исследования*

INTRODUCTION

The incidence of gonadotropin-dependent, or true precocious puberty (TPP) ranges from 1:5000 to 8:10,000 in the pediatric population. TPP is characterized with the appearance of secondary sexual characteristics in girls before the age of 8 years and in boys before the age of 9. Girls are significantly more often affected [1]. If organic pathology of the central nervous system (tumors, hamartomas, residual-organic lesions of the central nervous system (CNS)), as well as TPP stimulated by excessive sex steroids in congenital hyperplasia of the adrenal cortex is excluded, the cause of premature activation of the hypothalamic-pituitary-gonadal axis (HPGA) in 50 to 90% of cases remains unclear and is designated as idiopathic precocious sexual development [2].

A number of population studies have noted a correlation between the age of onset of puberty in children and their parents. Moreover, the timing of sexual development features (including menarche) is more consistent in monozygotic twins. The genetic regulation of HPGA involved in puberty has been actively studied [3–5].

In recent decades, there has been significant progress in the study of hereditary variants of TPP, which is primarily due to the expanding capabilities of molecular genetics. Emerging publications show that 25–27.5% of cases of gonadotropin-dependent TPP are familial forms of the disease, which have a monogenic nature [6].

Identification of genetic markers of TPP has shown that mutations in the *KISS1*, *KISS1R*, *MKRN3*, and *DLK1* genes are most often associated with premature activation of HPGA in childhood [2, 7].

The neuropeptide kisspeptin (KISS1 gene, cytogenetic localization of the gene — 1q32.1, OMIM no. 603286) is an endogenous ligand of the KISS1R receptor (GPR54 gene, cytogenetic localization — 19p13.3, OMIM no. 604161) [8].Kisspeptin binds to its receptor on hypothalamic and adeno-hypophysial neurons and stimulates the activity of these receptors. Kisspeptin is currently recognized as the most important regulator of puberty onset, sex hormone-mediated gonadotropin secretion, and fertility [9, 10].

The *MKRN3* gene is localized on the long arm of chromosome 15 (15q11.2, OMIM no. 603857) [8]. Mutations in the *MKRN3* gene are believed to be the leading mutation among familial forms of TPP. Geneticists believe that when this gene is mutated, abnormalities develop in cases when the defect is inherited in both paternal and maternal lines [11]. It is possible that *MKRN3* has a suppressive effect on gonadotropin-releasing hormone (GnRH)-secreting neurons during childhood, whereas its loss of function contributes to the activation of GnRH secretion and the premature onset of puberty [6]. Asymptomatic carriage of pathogenic variants of the gene has also been reported, confirming the possibility of incomplete penetrance [12].

TPP can be inherited by three mechanisms: autosomal dominant, autosomal recessive, and additive ones. These mechanisms depend on mutation that results in the manifestation of a certain disorder. The *MKRN3* and *DLK1* genes are characterized by an imprinting pattern of inheritance. Epigenetic modifications that alter the expression of these genes are also considered among the causes of precocious puberty [7]. *DLK1* (cytogenetic location: 14q32.2, OMIM no.176290) [8] is expressed from the father [13, 14].

Obviously, there is a special demand for genetic screening of children from families with an aggravated hereditary history of TPP.

Information about genes associated with TPP is being supplemented by other candidate genes: *MAPK8IP3* (OMIM no. 605431), *POU1F1* (OMIM no. 173110) and *NPFF1R* (cytogenetic location: 10q22.1, OMIM no. 607448) [6, 8]. *MAPK8IP3* gene is localized on the short arm of chromosome 16 (16p13) and is characterized by autosomal dominant type of inheritance. Heterozygous mutations of this gene are often associated with various variants of neurodevelopmental disorders, in 50% of cases combining with brain anomalies [15].

Both autosomal recessive and autosomal dominant types of inheritance can occur in TPP caused by a mutation of the *POU1F1* gene mapped on the short arm of chromosome 3 (3p11.2). Moreover, interaction of *POU1F1* with a number of transcription factors is necessary for targeted and selective differentiation of thyroid and gonadotropic cell lines of adenohypophysis. Therefore, pathogenic variants of *POU1F1* genes can also lead to deficiency of other adenohypophysis hormones [16].

The product of *NPFFR1* gene expression is a neuropeptide receptor that is localized on GnRH-secreting hypothalamic neurons. Aberrations in *NPFFR1* may also contribute to premature activation of HPGA.

Unfortunately, the method of genetic analysis of TPP is still in early use in our domestic clinical practice.

In case hypothalamic-sellar volumetric masses are detected, a neurosurgeon together with an endocrinologist decide whether neurosurgical intervention is necessary and appropriate.

In case of CNS neoplasms that do not require surgical treatment, as well as in all other cases of TPP, conservative therapy is indicated. The main goal of therapy for TPP is to suppress the development of secondary sexual characteristics that cause psychological discomfort and social difficulties for the child and his or her parents, as well as to normalize the rate of linear growth, slow the rate of ossification, and prevent stunting [1].

Prolonged GnRH analogs are used for the pharmacologic treatment of TPP [2]. Regular cyclic administration of luliberin agonists promotes desensitization of pituitary gonadotrophs and suppression of luteinizing hormone (LH), follicle stimulating hormone (FSH) secretion. As a result, there is a decrease in the formation of sex steroids in gonads. Such therapy is widely used in the world and has a long history (more than 30 years) [17, 18].

In the Russian Federation, the GnRH analog triptorelin has been registered and has been clinically tested. The drug is administered intramuscularly, the frequency of administration is once every 28 days. For children weighing less than 20 kg — 1.875 mg, more than 20 kg — 3.75 mg. There are prolonged analogs of GnRH in Russia. Triptorelin has a longer action, it is administered in 11.25 mg once every 12 weeks [2].

Both foreign and domestic publications have previously reported the high efficacy of this therapy by blocking the secretion of gonadotropic hormones and the progression of puberty [19–21].

In some countries, an implant with a GnRH agonist, histrelin (Supprelin) is inserted, its effect lasts for 1 year [22, 23]. However, this requires surgical intervention and regular monitoring of efficacy. After 12 months, the current implant should be removed and replaced with another to continue treatment. Permission to use this method in domestic medicine has not yet been obtained.

The question of whether the long-term use of suppressive therapy with gonadoliberins in TPP can affect puberty remains relevant for practical health care. The effects of these drugs with respect to final growth, timing of therapy completion and recovery of the hypothalamic-pituitary axis, and safety of therapy are debated.

AIM

To study pubertal maturation in girls after completion of cyclic suppressive therapy for TTP with triptorelin.

MATERIALS AND METHODS

There have been analyzed medical records of 17 girls with TPP. All girls were examined in the endocrinology department of St. Petersburg State Pediatric Medical University and received cyclic suppressive therapy with triptorelin until the age of 12 years.

All patients aged 3–8 years were diagnosed with TPP based on the characteristic clinical picture and the results of the test with a synthetic short-acting GnRH analog. After the exclusion of a volumetric mass based on the results of magnetic resonance imaging of the brain with pituitary contrasting, TPP of central genesis was considered idiopathic, and suppressive therapy with triptorelin was prescribed. The drug administration regimen was cyclic, according to the clinical recommendations that were valid at the time of treatment [2]. After the start of therapy blocking LH and FSH secretion, all patients underwent regular monitoring by an endocrinologist, including in-depth examination in an endocrinologic hospital once a year. Therapy with GnRH analogs had an effective and persistent effect on suppressing puberty: it led to a decrease in the volume of breast glands, regression of sexual characteristics, and disappearance of menstruation. In addition, the effectiveness of the therapy was evidenced by the results of ultrasound examination of the pelvic organs (uterus and ovaries volume reduction, decrease in the size and number of follicles), inhibition of bone age. LH, FSH, estradiol levels reached pre-pubertal values. It should be noted that the parents of four girls also entered puberty

early. The duration of GnRH treatment depended on the age when secondary sexual characteristics appeared and the time therapy was started. All children completed therapy at the age of 12 years.

An online questionnaire was administered to girls. It contained questions about puberty, estimated growth estimation, menstrual timing after drug withdrawal, and family history of pubertal onset in relatives. The age of the girls at the time of interview ranged from 12 years 9 months to 17 years 4 months.

Patients were divided into two groups according to the duration of triptorelin therapy: Group 1 (58.8%) received the drug for less than 5 years (from 1 year to 4 years 3 months), Group 2 (41.2%) – from 5 years and up to 7 years 10 months. The growth of the patients was analyzed according to standard deviations. Height within ±1 SDS was considered average; ±1 to ±2 SDS was considered above and below average, respectively; more than –2 SDS was considered stunted and more than +2 SDS was considered tall. The time of onset of menstruation was determined.

RESULTS

Follow-up monitoring of the patients after discontinuation of treatment indicated a gradual recovery of gonadal function, manifested by enlargement of breast glands, progression of pubic and axillary hair loss. After discontinuation of triptorelin therapy, menstruation started in 6 months in 23.5% of the patients, including 17.6% in Group 1 and 5.9% in Group 2. The onset of menstruation in the period from 6 months to 1 year after the end of treatment was noted in 52.9% of patients, including 35.3% in Group 1 and 17.6% in Group 2. Later onset of periods (1.5-2 years later) was observed in 17.6% of patients, including 5.9% in Group 1 and 11.8%

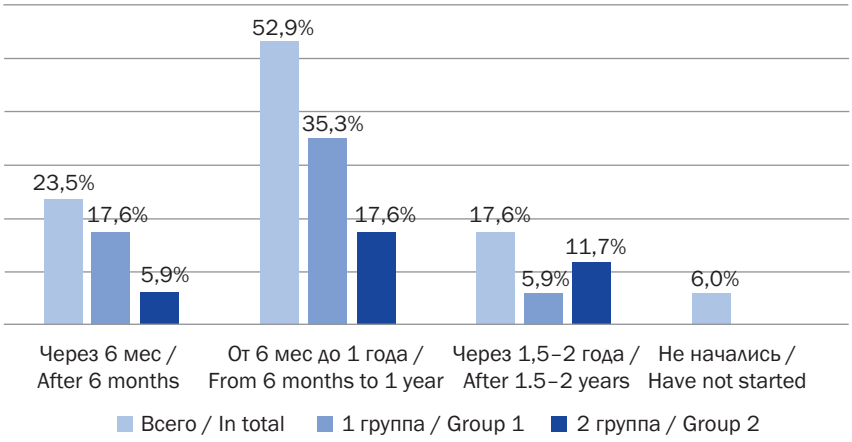

Fig. 1. The appearance of menarche depending on the duration of suppressive therapy

Рис. 1. Появление менархе в зависимости от продолжительности супрессивной терапии

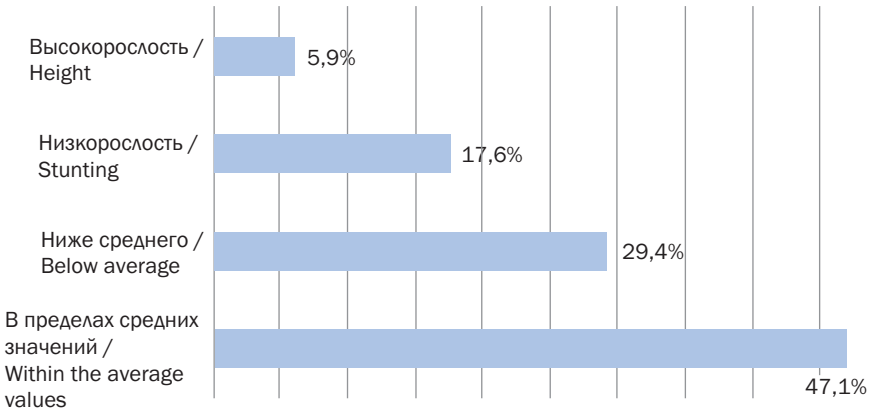

Fig. 2. Growth at the time of the survey

Рис. 2. Рост на момент анкетирования

in Group 2 (Fig. 1). One girl aged 16 years had no menstruation, which was explained by polycystic ovary syndrome (PCOS) diagnosed during the examination.

The relatively later development of menstrual function in girls who received GnRH suppressive therapy for more than 5 years (in group 2) can be associated with the fact that after longer treatment the body needs more time to restore the natural cycle of hormonal regulation.

The height of the patients at the time of the questionnaire was within average values in 47.1% of girls, below average in 29.4%, low height in 17.6%, and high height in 5.9% of patients (Fig. 2).

Girls who started triptorelin suppressive therapy within the first year of the TPP onset (64.7%) showed average growth in 54.5% of cases, below average growth in 36.4%, and stunting in 9.1% of cases. At a later start of therapy, 2-3 years after the first signs of TPP (35.3%), average height was observed in 33.3% of patients, below average — in 16.7%, stunting — in 33.3% of patients, and in one case high stature was observed (Fig. 3).

When treatment duration was less than 5 years, 30% of the patients had average height, 30% had height below average, 30% had stunting, and 10% had high stature. In case of prolonged therapy (more than 5 years), average height was registered in 71.4% of the patients in this group, below average — in 28%, stunting was not registered (Fig. 4).

Clinical peculiarities of sexual development after completion of triptorelin treatment prove reversibility of an antigonadotropic effect of triptorelin. The function of sex glands is successfully restored after the end of treatment. However, one of the observed patients aged 16 years had no menstruation, and during the examination she was diagnosed with polycystic ovary syndrome, primary amenorrhea, normogonadotropic ovarian dysfunction, normoprolactinemic variant. Further, this patient was initiated treatment with a contraceptive combined drug (estrogen+gestagen) with antiandrogenic effect by a gynecologist.

Longer-term results (ovulation, fertility) in individuals who received suppressive therapy with triptorelin in childhood have not yet been sufficiently studied due to the lack of a long follow-up period [22–24]. Nevertheless, it is important to understand the long-term outcomes of suppressive therapy and TPP. Medical literature has reported pregnancy in women treated with GnRH [25, 26].

Thus, the problem of TPP in girls is extremely important since this condition and the choice of its treatment may affect the future reproductive function of female

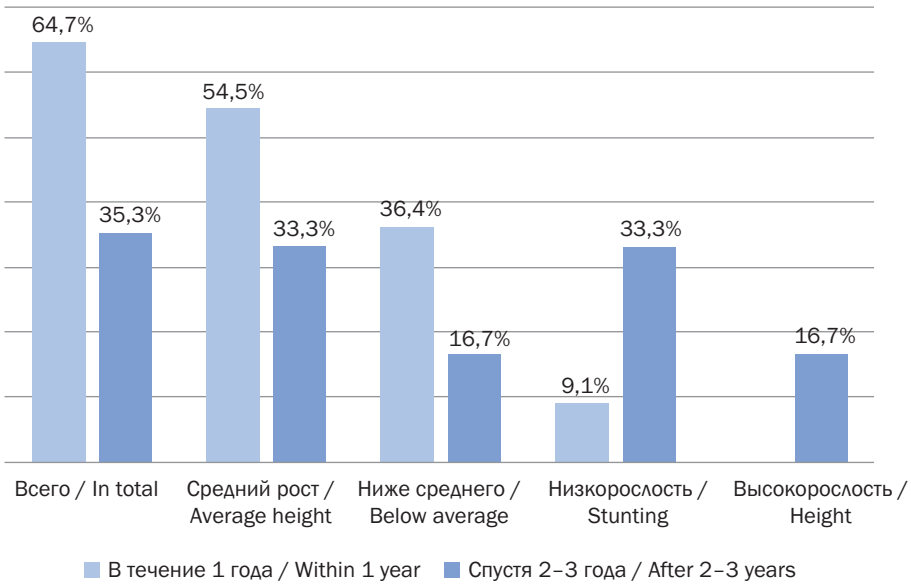

Fig. 3. The dependence of growth on the time on the initiation of therapy after the appearance of the first signs of precocious puberty

Рис. 3. Зависимость роста от времени начала терапии после появления первых признаков преждевременного полового развития

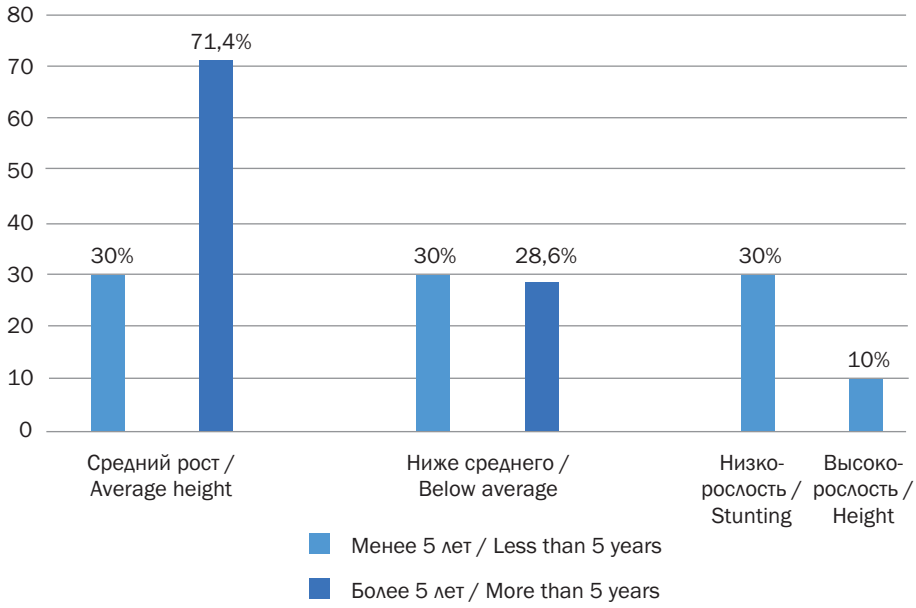

Fig. 4. The dependence of growth on the duration of treatment

Рис. 4. Зависимость роста от длительности лечения

patients. The lack of data regarding associated pathogenic genes in the examined patients with TPP necessitates further inclusion of a molecular genetic study to verify possible causes of TPP.

CONCLUSION

Clinical manifestations of sexual development in female patients after completion of triptorelin treatment prove the reversibility of an antigonadotropic effect of triptorelin. The menstrual cycle establishment occurs later after treatment withdrawal in those who used the drug for more than 5 years. Timely initiation of TPP treatment helps to avoid stunting in the majority of patients. Molecular genetic study is advisable to verify the genesis of TPP, given the high frequency of familial forms of this disease. It is important to know the long-term results of using suppressive therapy for TPP and its possible impact on the reproductive period of patients' life.

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.

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ALLERGIC REACTIONS TO ANTITUBERCULOSIS DRUGS IN CHILDREN: DIAGNOSTIC POSSIBILITIES

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ABSTRACT. ***Introduction.*** Chemotherapy for tuberculosis in children is often difficult due to poor tolerability. ***The goal of the study*** is to determine the frequency and spectrum of allergic adverse reactions during chemotherapy for tuberculosis in children and to substantiate the method of their laboratory diagnostics. ***Materials and methods.*** We carried out a cohort retrospective study (from 2018 to 2021) which included 146 patients and a prospective study (from 2022 to 2024) of 50 patients. All 196 children (0–14 years) received the intensive phase anti-tuberculosis chemotherapy with a combination of 3–4 drugs. ***Results.*** A retrospective analysis showed that there were no adverse reactions in 56 (38.3%) children, allergic reactions were observed in 32 (21.9%), toxic-allergic reactions in 22 (15.1%), and toxic reactions in 36 (24.7%). In a prospective study in 50 children underwent a basophil activation test using flow cytometry for the drugs they were receiving (196 tests in total). Most basophil activation tests were performed for first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide — 178 (90.8%), for second-line drugs 18 (9.2%). Of the 196 tests, 38 (19.4%) gave a positive result. The test results were compared with the clinical manifestations of adverse reactions in three groups of patients: group I — 18 children with allergic and toxic-allergic reactions to antituberculosis drugs, group II — 14 patients with toxic reactions, group III — 18 children without adverse reactions. In group I the proportion of patients with a positive result of the basophil activation test (for 1 or 2 drugs) was 94.4%, which is higher than in group II — 71.1% and significantly higher than in group III — 16.7% ($P < 0.05$; $\chi^2 = 54.9$). ***Conclusion.*** The importance of the basophil activation test in predicting allergic and toxic-allergic reactions and determining the drug responsible for side effects during combination chemotherapy has been proven.

KEYWORDS: *children, tuberculosis chemotherapy, allergic adverse reactions, basophil activation test*

АЛЛЕРГИЧЕСКИЕ РЕАКЦИИ НА ПРОТИВОТУБЕРКУЛЕЗНЫЕ ПРЕПАРАТЫ У ДЕТЕЙ: ВОЗМОЖНОСТИ ДИАГНОСТИКИ

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РЕЗЮМЕ. ***Введение.*** Химиотерапия туберкулеза у детей часто бывает затруднена из-за явлений плохой переносимости. ***Цель исследования*** — определить частоту и характер аллергических нежелательных побочных реакций при химиотерапии туберкулеза у детей, обосновать метод их лабораторной диагностики. ***Материалы и методы.*** Проведены когортное ретроспективное исследование (с 2018 по 2021 гг.), в которое включены 146 пациентов, и проспективное исследование (с 2022 по 2024 гг.) — 50 пациентов. Все дети (0–14 лет) получали интенсивную фазу противотуберкулезной химиотерапии комбинацией 3–4 противотуберкулезных препаратов. ***Результаты.*** Ретроспективный анализ показал, что нежелательные побочные реакции отсутствовали у 56 (38,3%) детей, аллергические реакции наблюдались у 32 (21,9%), токсико-аллергические у 22 (15,1%), токсические у 36 (24,7%) детей. В проспективном исследовании 50 детям выполнен тест активации базофилов методом проточной цитометрии на те препараты, которые они получали (в целом 196 тестов). Большинство тестов активации базофилов выполнены на препараты первого ряда (изониазид, рифампицин, этамбутол, пиразинамид — 178 (90,8%), на препараты второго ряда — 18 (9,2%)). Из 196 тестов положительный результат дали 38 (19,4%). Результаты тестов сопоставлены с клиническими проявлениями нежелательных побочных реакций в трех группах пациентов: I группа — 18 детей с аллергическими и токсико-аллергическими реакциями на противотуберкулезные препараты, II группа — 14 пациентов с токсическими реакциями, III группа — 18 детей без нежелательных реакций. В I группе доля пациентов с положительным результатом теста активации базофилов (на 1 или 2 препарата) составила 94,4%, что выше, чем во II группе — 71,1% и значительно выше, чем в III группе — 16,7% ($P < 0,05$; $\chi^2 = 54,9$). ***Заключение.*** Доказано значение теста активации базофилов в прогнозировании аллергических и токсико-аллергических реакций и определении препарата — виновника нежелательных побочных реакций при комбинированной химиотерапии.

КЛЮЧЕВЫЕ СЛОВА: *дети, химиотерапия туберкулеза, аллергические нежелательные побочные реакции, тест активации базофилов*

INTRODUCTION

Monitoring of tuberculosis epidemic situation in the Russian Federation has shown that after a decrease in incidence in children 0-14 years of age in 2013–2020, the indicator stagnates at 6.7 per 100,000 in the following years [1], which requires increased attention to all aspects of pediatric tuberculosis, including its treatment [2].Undesirable adverse reactions (UARs) resulting from the use of antituberculosis drugs (ATDs) in children can significantly complicate the course of tuberculosis chemotherapy and reduce its effectiveness [3, 4]. UARs for antituberculosis drugs in children, as well as adults, are divided into toxic, allergic, and toxic-allergic ones according to mechanisms of origin [5, 6].

Toxic UARs are organ-specific and depend on the dose, structure and metabolism which is specific for each TB drug. For example, isoniazid, cycloserine, prothionamide have toxic effects on the nervous system; aminoglycosides are ototoxic and nephrotoxic, many ATDs have hepatotoxic effects, etc.

Allergic UARs are hypersensitivity reactions. They can occur with any TB drug, regardless of the dose. From a practical point of view, it is difficult to identify the drug that caused an allergic reaction in combination chemotherapy, and it is often necessary to cancel all drugs.

Toxic-allergic adverse reactions occur when an allergic state develops, which is accompanied by a vascular reaction, enzymatic and biochemical shifts that aggravate the toxic effect of drugs on organs and tissues.

According to literature data, allergic adverse reactions during TB treatment in children account for 20–30% [7], while toxic and toxic-allergic reactions predominate. However, some studies emphasize the high frequency of adverse reactions of allergic genesis (50.5%) is a peculiarity of childhood [8]. Allergic reactions are often manifested by isolated eosinophilia, as well as skin reactions in the form of rashes and itching, are often systemic, and may be accompanied by organ damage, fever [9]. Therefore, they are often treated as toxic-allergic and toxic, thus, it is not possible to identify the allergic factor in the development of UARs using routine methods.

The main method of drug allergy detection is pharmacological anamnesis, but it is usually difficult to apply it in newly diagnosed tuberculosis patients. Taking into account multicomponent chemotherapy regimens for tuberculosis, it can be quite difficult to identify the drug responsible for drug allergy [10]. The methods of recording allergic reactions to ATDs are underdeveloped and there are few studies based on the general principles of drug allergy diagnosis [11]. *In vivo* tests — patch-test [12], provocation test [13] — can cause aggravation of allergic reactions up to life-threatening conditions, which is why their use is limited. The advantages of *in vitro* tests over *in vivo* diagnostic tests are their safety, as well as the possibility to test several drugs simultaneously [14]. Allergic reactions to ATDs have been determined by lymphocyte blast-transformation reaction (LTR), initially by staining smears with azur-2-eosin [15, 16], and in later studies the proliferative activity of lymphocytes was determined by the incorporation of H3-thymidine into cell DNA [17, 18]. The method did not find further application in phthisiatric practice. One publication mentions the use of leukocyte agglomeration reaction to detect allergy to rifampicin and kanamycin [19]. In order to diagnose drug allergy to some antibacterial drugs, the determination of allergen-specific IgE antibodies to the corresponding allergens is used. However, kits for the determination of specific IgE are only available for a limited number of drugs, including amoxicillin, ampicillin, cefaclor, and penicillin [20]. In addition, only IgE-mediated allergy is detected using allergen-specific IgE antibodies, whereas it can be caused by different mechanisms (IgE-mediated and non-IgE-mediated) [21].

The basophil activation test (BAT) is a promising and sought-after method of allergy diagnosis, which makes it possible to detect a reaction to any drug. The great advantage, especially in comparison with diagnostic tests of allergen-specific IgE determination, is that BAT evaluates both IgE-dependent and IgE-independent mechanisms of allergy [22–25]. The basophil activation test is based on the contact of allergen with various receptors on the basophil membrane (including the IgE-FcεRI complex) with activation of a range of enzymatic reactions [26]. Activation of basophils leads not only to the release of soluble mediators, but also to the expression of activation markers — CD63

and CD203c — on the membrane, which are taken into account using flow cytofluorimetry [27, 28]. When diagnosing drug allergy to some antibiotics in patients, the sensitivity varies from 33 to 67%, and the specificity of this method varies from 79 to 100%, which indicates that it is promising, according to a number of authors [14, 29, 30].

AIM

To determine the frequency and nature of allergic UARs during chemotherapy of tuberculosis in children, to substantiate the method of their laboratory diagnostics.

MATERIALS AND METHODS

The study is cohort, retrospective and prospective. It covered the period from 2018 to 2024. The study was carried out on the basis of the tuberculosis department of the St. Petersburg State Budgetary Institution "Children's Infectious Diseases Hospital No. 3" (DIB NO. 3). Overall, 196 children with active forms of respiratory tuberculosis were included.

Inclusion criteria were: presence of active respiratory tuberculosis; full intensive phase (IP) of chemotherapy (CT) in the pediatric tuberculosis department; absence of parasitic invasions. Exclusion criteria: inactive tuberculosis or latent tuberculosis infection; leaving the hospital before the end of IP chemotherapy; parasitic invasions detected before or during treatment. The age of children varied from 0 to 14 years inclusive. Girls constituted 106 (54.1%), boys — 90 (45.9%). Children of early age (from 0 to 3 years) accounted for 31 (15.8%), from 3 to 7 years — 84 (42.8%), from 8 to 14 years — 81 (41.4%).

The research was conducted in two stages. The first stage (retrospective) included the analysis of archived case histories of 146 children for 2018–2021 in order to determine the number of all ARDs when taking ATD. The frequency and spectrum of reactions caused by allergic and toxic-allergic mechanisms were defined. The second stage (prospective) involved the observation of children (50 patients) during the course of the study, recording UARs and performing the basophil activation test.

Patients were examined according to the Clinical Recommendations that were relevant for the period of the study [31]. Examination was conducted before the administration of chemotherapy (CT) for tuberculosis and in the course of dynamic follow-up. It included: anamnesis collection (epidemiological, social, allergological, pharmacological ones); physical examination methods, standard clinical and biochemical blood and urine tests, chest computed tomography, immunodiagnostics using Mantoux test with 2 units and test with recombinant tuberculosis allergen (RTA, Diaskin-test). Bacteriological studies aimed at detection of Mycobacterium tuberculosis (MBT) included sputum smear microscopy (or bronchoscopy), molecular genetic methods of pathogen detection, culture on dense and liquid growth-supporting microenvironment. Fibrobronchoscopy and test for interferon-gamma induction by MBT antigens (TB-Feron test) were performed when indicated. Triple stool tests for helminth eggs and parasites were performed. All children underwent electrocardiography (ECG) and pulmonary function tests. In the course of chemical treatment, a clinical blood test, urine analysis, extended blood biochemical analysis with determination of alanine and asparagine transaminases (ALT and AST), bilirubin, uric acid and other indices of liver and kidney function were performed once a month (more often if indicated) to monitor possible UARs to the drugs.

The basophil activation test via flow cytometry was used as a special method for diagnosing sensitization to drugs. BAT with drugs was performed within 2 hours from the moment of blood collection in vacutainers with lithium heparin. Allergenicity kit (Beckman-Coulter) was used to perform the test by flow cytometry. According to the instructions for the test system, the basophil population was detected in a multicolor protocol with multistage gating using monoclonal antibodies to CD3, CD294, CD203c. Cell activation was assessed in vitro based on the increase in CD203c expression after drug stimulation. The technique of basophil activation test (BAT) was as follows [32]. Since tested TB drugs were in tablet form (except amikacin), a contact aqueous solution based on the drug and distilled water was used. Supernatant from the prepared drugs was used at a dilution of 1:25 in relation to the

patient's blood sample. Presence/absence of sensitization to drugs in BAT was determined on the basis of basophil activation index with a threshold value of 1.1. The basophil activation index is the ratio of the number of activated basophils in the sample with allergen to the number of these cells in the sample with buffer solution.

All 50 children included in the prospective study got through BAT for those drugs, which they received according to the regimen of ChT, in order to diagnose sensitization of the organism to antituberculosis drugs. The study was performed 2 weeks after the therapy had started. 46 out of 50 children were tested for sensitization to 4 drugs and 4 children – to 3 drugs. The follow-up period lasted for 2 months. ChT prescription, monitoring and evaluation of possible adverse reactions were performed according to the Federal Clinical Guidelines "Tuberculosis in Children" (2018, 2020, 2022).

Statistical processing. The database was composed in Excel 2010 program (Microsoft Office). Differences between relative values were determined using the Pearson χ^2 criterion in STATISTICA 6.1. The generally accepted confidence level of 95% ($p < 0.05$) was considered. The odds ratios (ORs) for the development of UARs and their 95% confidence interval (95% CI) were determined.

The study was approved by the local ethical committee of the St. Petersburg State Pediatric Medical University, conclusion No. 06/04 dated 02.12.2021.

RESULTS

The retrospective study revealed that 146 children who received inpatient TB treatment in 2018–2022 had the following clinical forms of the disease: intrathoracic lymph node tuberculosis (ITNT) – 103 (70.5%), primary tuberculosis complex (PTC) – 35 (24.0%), infiltrative TB- 5 (3.4%), focal TB – 2 (1.3%), disseminated TB – 1 (0.7%). Only 2 children had their own bacterial excretion (MBT sensitivity to ATDs was preserved), so chemotherapy regimens (ChTR) were prescribed on the basis of information about the MBTs of an adult patient with whom the child was in contact. Standard I/III chemotherapy regimens consisting of four main ATDs (isoniazid, rifampicin, ethambutol, pyrazinamide) were given to 124 children (84.9%). If multidrug-resistant (MDR) MBT was found, children were treated with IV ChTR (22 (15.1%) children in total). A combination of 4–5 ATDs was administered as part of IV ChTR (22 children), taking into account the source MBT resistogram. 56 (38.3%) out of 146 examined children had no adverse effects during therapy, while the remaining 90 children had adverse effects, the spectrum of which is shown in Figure 1.

Thus, three types of adverse reactions to TB drugs could be distinguished.

Allergic reactions were observed in 32 (21.9%) children. Isolated eosinophilia prevailed – 26 (81.2%). It constituted 7–10% of cells in the leukocytic formula (up to 500 cells in μl of blood) – in 15 people, 10–19% (500–1500 cells in μl) – in 8 people, 20% and more (more than 1500 cells in μl) – in 3 people. In addition to isolated eosinophilia, it was combined with other manifestations of allergy (skin rashes, bronchospasm, rhinitis, conjunctivitis) in 4 (12.5%) children. Cutaneous allergic reactions (urticaria, pruritus) without eosinophilia occurred in 6.3% (2 people).

Toxic-allergic reactions occurred in 22 (15.1%) patients. Allergic symptoms in the form of eosinophilia were combined with dysfunction of various organs. Increased serum levels of liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) were additionally observed among 13 (59.1%) children. 4 (18.3%) patients had elevation of uric acid. Increased levels of enzymes combined with hyperuricemia was observed in 5 (22.7%) patients. Elevation of liver enzymes up to 1.5 norms was observed in

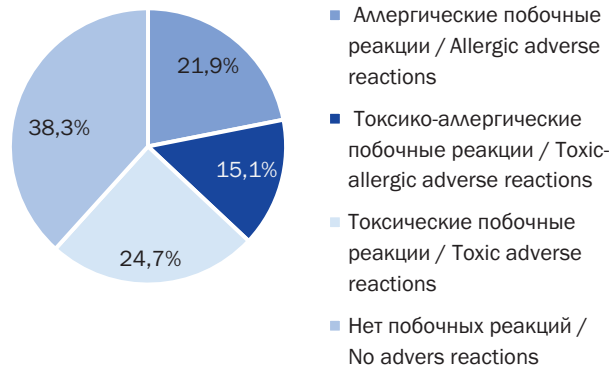

Fig. 1. Structure of adverse reactions during tuberculosis chemotherapy in 146 children

Рис. 1. Структура нежелательных побочных реакций при химиотерапии туберкулеза у 146 детей

6 (27.2%), from 1.5 to 3 norms — in 4 (13.6%), over 3 norms — in 3 (9%) children. In addition to these laboratory shifts, some of these children had clinical symptoms in the form of skin manifestations (urticaria, dermatitis, itching) — 4 children (18.2%), joint pain — 1 (4.5%), dyspeptic phenomena (vomiting, nausea, abdominal pain) — 5 (22.7%), central nervous system manifestations — 4 (18.2%) (sleep disturbance — 1, photophobia — 1, hyperexcitability — 1, auditory hallucinations — 1).

Toxic reactions without allergy manifestations were registered in 36 children (24.7%). Elevation of liver enzymes was the main manifestation of toxic UARs, it was found in all children of this group 36 (100%). Liver hyperfermentemia was combined with hyperuricemia in blood biochemical analysis in 17 (47.2%) cases, dyspeptic phenomena — in 10 (27.7%) children, neurotoxic reactions — in 4 (11.1%) patients, one case each — nest alopecia, color perception disorders, nosebleeds.

All UARs were reversible on the background of symptomatic treatment, however, temporary withdrawal or replacement of drugs was required in allergic UARs in 8 (25.0%) cases, in toxic-allergic reactions — in 10 (45.5%) cases ($P < 0.05$).

Thus, the retrospective analysis allowed us to conclude that the allergic mechanism is significant in the development of adverse reactions during chemotherapy of tuberculosis in children, since purely toxic UARs without allergic manifestations were less frequent (24.7%) than reactions with clinical and laboratory signs of increased sensitization to the drugs, which were observed in 37% of children. Among them, allergic reactions were registered in 21.9% of children and toxic-allergic reactions in 15.1%. Development of laboratory tests allowing to determine the level of sensitization of a child's organism to TB drugs is in demand in clinical practice. The prospective part of the study is focused at solving this problem.

50 children participating receiving intensive phase of chemotherapy in 2022-2023 were diagnosed with the following clinical forms of tuberculosis: uncomplicated intrathoracic lymph node tuberculosis (ITNT) — 17 (34.0%), complicated ITNT — 13 (26.0%), primary tuberculosis complex (PTC) — 9 (18.0%), infiltrative TB — 2 (4.0%), focal TB — 3 (6.0%), disseminated TB — 4 (8.0%), tuberculous pleurisy — 2 (4.0%). The structure of complicated ITNT (26.0%) included: foci of dropouts in the lung tissue — 10 (20.0%), bronchial tuberculosis 2 (4.0%) and bronchopulmonary lesions — 1 (2.0%). The vast majority of children — 45 (90.0%) — received I/III ChTR, which included the main 1st-line TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). In isolated cases, II ChTR (in case MBT was resistant to isoniazid, 2 children), and IV ChTR (in case of multidrug-resistant MBT, 3 children) were prescribed; these regimens included reserve TB drugs prescription in accordance with the current clinical recommendations.

Analysis of chemotherapy tolerance showed that only 18 (36.0%) children had no UARs. 7 (14.0%) children developed allergic UARs, 11 (22.0%) had toxic-allergic UARs and 14 (28.0%) suffered from toxic UARs. Other reasons for allergic reactions (except TB drugs) were excluded according to the anamnesis, clinical and laboratory data obtained by the moment of the research. Thus, the ratio of UARs types in the prospective study coincided with the retrospective one. 50 children were divided into three groups according to the presence or absence of UARs.

- Group I (18 (36.0%)) — children with allergic and toxic-allergic reactions to the drugs administered;
- Group II (14 (28.0%)) - children with toxic reactions without allergic manifestations;
- Group III (18 (36.0%)) - children without undesirable adverse reactions to the drugs.

Clinical and laboratory manifestations of UARs in children of groups I and II are presented in Figures 2 and 3.

The number of BATs performed as well as their results are presented in Table 1. A total of 196 tests were performed, mainly for 1st-line drugs — 178 (90.8%), in isolated cases for 2nd-line drugs — 18 (9.2%) (for children receiving II and IV RCTs). Positive results of BAT (presence of sensitization to drugs) were obtained in 38 tests out of 196 (19.4%). The most frequent positive BAT results were for rifampicin (23.9%) and ethambutol (23.4%), while isoniazid (9.3%) was the least frequent (Table 1).

20 patients (40.0%) out of 50 children tested had negative BATs for all drugs taken. There were

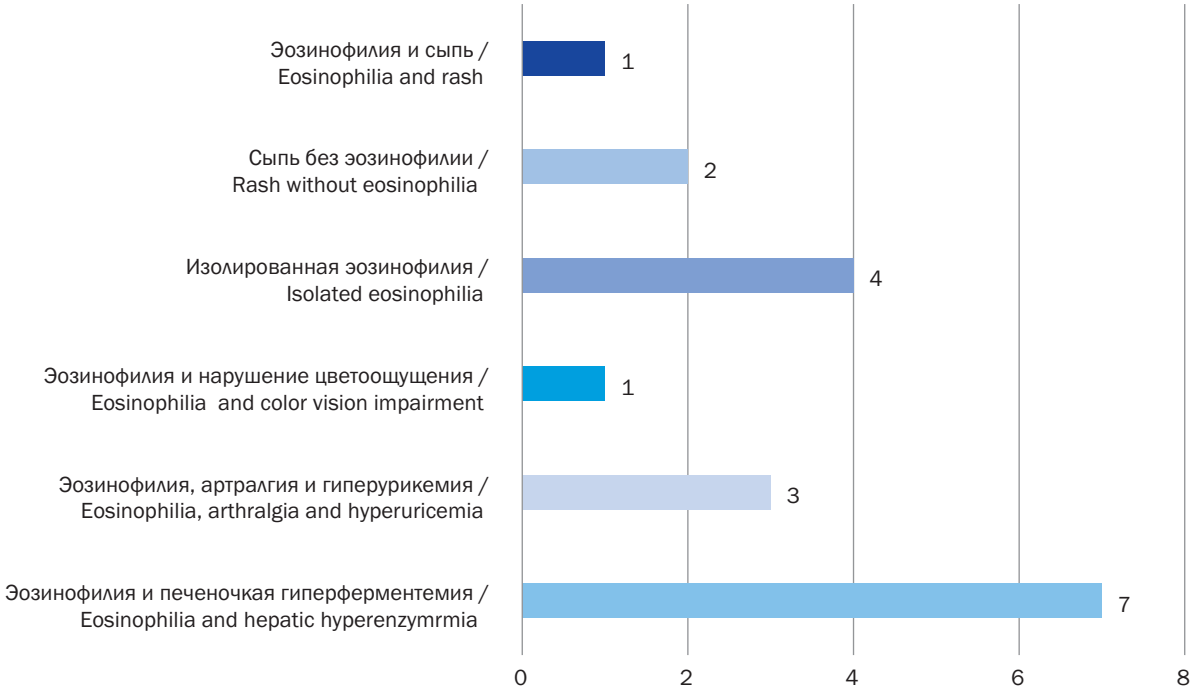

Fig. 2. Manifestations of allergic and toxic-allergic advers reactions to antituberculosis drugs, I group of children (n=18)

Рис. 2. Проявления аллергических и токсико-аллергических побочных реакций на противотуберкулезные препараты, I группа детей (n=18)

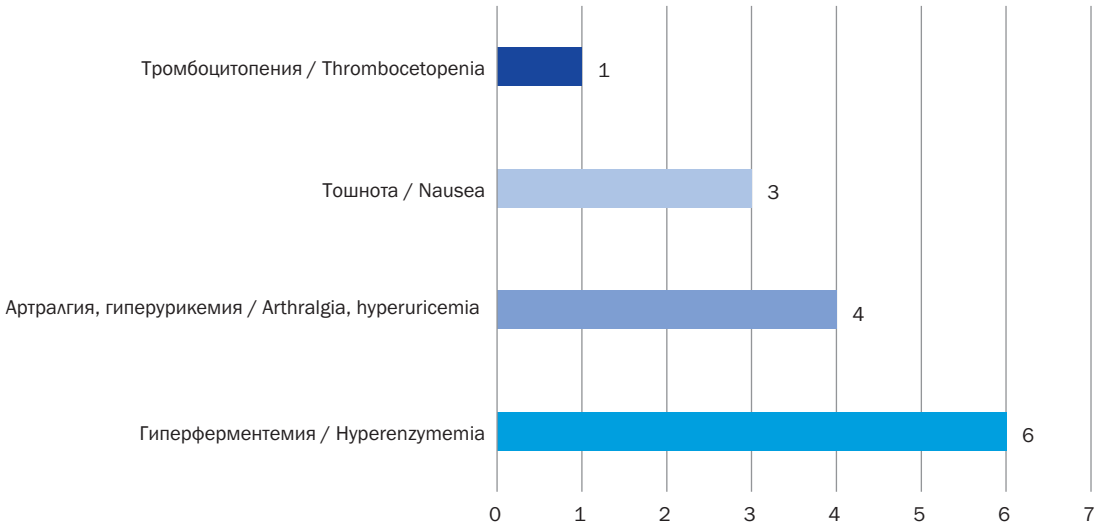

Fig. 3. Manifestations of toxic advers reactions to antituberculosis drugs, II group of children (n=14)

Рис. 3. Проявления токсических побочных реакций на противотуберкулезные препараты, II группа детей (n=14)

30 (60.0%) children with positive BAT results, including BAT positive to one drug in 22 cases (44.0%) and positive to two drugs (8, or 16.0%).

When analyzing the results in three groups (Fig. 4), it turned out that negative BATs were significantly more frequent in Group III (without UARs). It amounted to 15 children (83.3%, P <0.05), Group I demonstrated a negative BAT test in 1 child (5.6%) and Group II — in 4 (28.6%) children. Accordingly, group III was significantly less likely to have positive BATs to both one and two ATDs (P <0.05). Group I which consisted of children with allergic and toxic-allergic reactions to antituberculosis drugs, included 94.4% children with positive BATs (to one or two drugs), which was higher than in group II

Table 1. Results of testing sensitization to antituberculosis drugs using the basophil activation test

Таблица 1. Результаты тестирования сенсибилизации к противотуберкулезным препаратам методом теста активации базофилов

Препарат / Drugs	Количество тестирований / Number of tests	Число положительных результатов / Number of positive results	Доля положительных результатов, % / Percentage of positive results, %
Изониазид / Isoniazid	43	4	9,3
Рифампицин / Rifampicin	46	11	23,9
Пиразинамид / Pyrazinamide	48	10	20,8
Этамбутол / Ethambutol	41	10	23,4
Амикацин / Amikacin	7	2	28,6
Левофлоксацин / Levofloxacin	4	1	25,0
Циклосерин / Cycloserine	2	0	0
Парааминосалициловая кислота / Para-aminosalicylic acid	2	0	0
Линезолид / Linezolid	2	0	0
Протионамид / Prothionamide	1	0	0
Всего / Total	**196**	**38**	**19,4**

(toxic UARs only) with 71.1% of positive BATs (P=0.07; χ^2=3.3) and significantly higher than in group III (without UARs) where positive BAT was observed in 16.7% of children (P <0.05; χ^2=54.9).

When comparing the number of positive tests for individual drugs, it was found (Table 2) that group I had the most frequent positive tests for ethambutol 42.9% (6 out of 14 tests were positive) and rifampicin 35.3% (6 out of 17 tests were positive). Positive BAT for pyrazinamide was the most frequent (46.2%) in group II. It should be noted that positive BAT results in group with no UARs were observed in 5.6% (4 positive tests out of 70), which is significantly rarer compared to both group I (31.4%, P <0.05) and group II (21.4%, P <0.05).

Odds ratio (OR) of UAR development was calculated in group I (18 children) (reactions presented) and group III (18 children) (no UAR) in order to study the prognostic value of BAT for allergic (allergic and toxic-allergic) UAR development. Calculation of the odds ratio (Table 3) showed that a positive BAT test in a child resulted in an 85-fold higher chance of clinical and laboratory manifestations of allergy (confidence interval 7.9–906.8). Since the lower limit of the 95% confidence interval is greater than 1, this result is reliable.

The sensitivity and specificity calculation of the test in predicting allergic manifestations showed the following results. Group I (18 children) which consisted of children with clinical manifestations of allergic and toxic-allergic reactions to TB drugs had positive basophil activation test in 17/18 children, i.e. 94.4% sensitivity of the test. Group III (18 children) did not have clinical manifestations of allergic reactions to TB drugs. The basophil activation test in the 3rd Group was negative in 15/18 children, or 83.3% specificity.

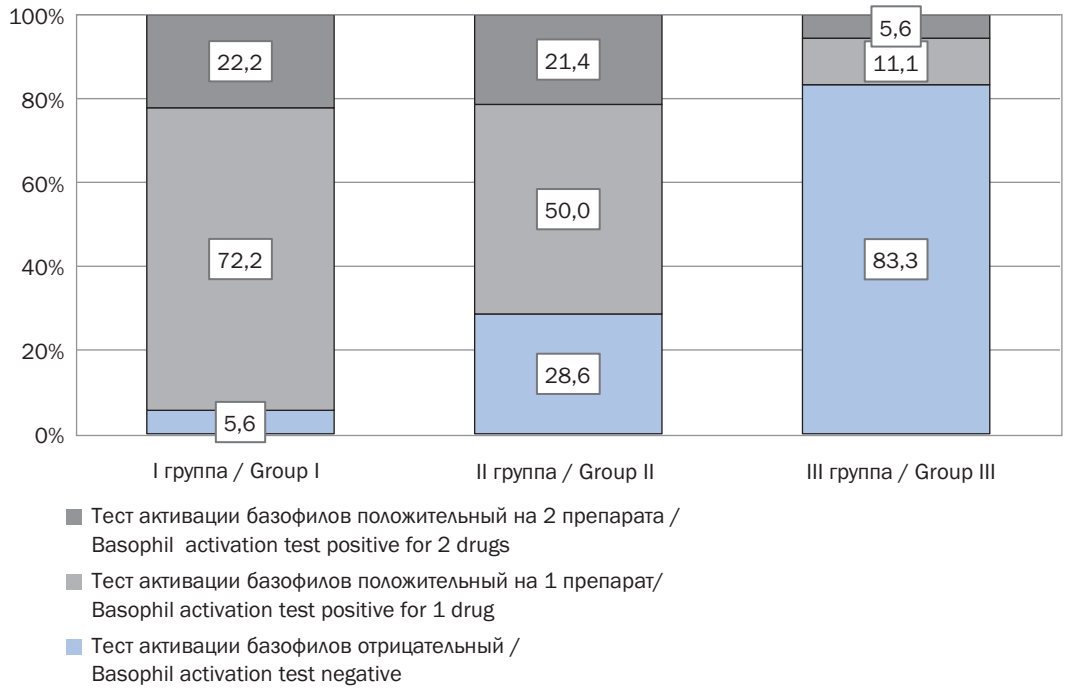

Fig. 4. Proportion of children with positive and negative basophil activation test results in three patient groups

Рис. 4. Доля детей с положительными и отрицательными результатами теста активации базофилов в трех группах пациентов

Table 2. The proportion of positive results of the basophil activation test in groups of children

Таблица 2. Доля положительных результатов теста активации базофилов в группах детей

Препарат / Drugs	I группа / I group	II группа / II group	III группа / III group
Изониазид / Isoniazid	3/14 (21,4%)	1/13 (7,7%)	0/16 (0%)
Рифампицин / Rifampicin	6/17 (35,3%)	4/13 (30,8%)	1/16 (6,3%)
Пиразинамид / Pyrazinamide	4/17 (23,5%)	6/13 (46,2%)	0/18 (0%)
Этамбутол / Ethambutol	6/14 (42,9%)	1/13 (7,7%)	3/14 (21,4%)
Амикацин / Amikacin	2/3	0/2	0/2
Левофлоксацин / Levofloxacin	1/2	0/1	0/1
Циклосерин / Cycloserine	0/1	–	0/1
Парааминосалициловая Кислота / Para-aminosalicylic acid	0/1	–	0/1
Линезолид / Linezolid	0/1	–	0/1
Протионамид / Prothionamide	–	0/1	–
Всего /Total	22/70 (31,4%)	12/56 (21,4%) P_{II-III}= 0,17; χ^2=1,89	4/70 5,6% P_{I-III}= 0,00008; χ^2=15,5

Table 3. The odds ratio of developing allergic and toxic-allergic reactions depending on the results of the basophil activation test

Таблица 3. Отношение шансов развития аллергических и токсико-аллергических реакций в зависимости от результатов теста активации базофилов

Группа пациентов / Patient group	Результаты теста активации базофилов (число детей) / Basophil activation test results (number of children)		Всего / Total	Отношение шансов (95% доверительный интервал) / Odds ratio (95% confidence interval)
	положительный / positive	отрицательный negative		
I группа (аллергические и токсико-аллергические реакции) / I group (allergic and toxic-allergic reactions)	17	1	18	85,0 (7,9–906,8)
III группа (нежелательные побочные реакции отсутствуют) / III group (advers reactions are absent)	3	15	18	

However, specificity may increase with extended follow-up time, as sensitization does not always manifest itself with allergic reactions.

CASE HISTORY 1

Girl S., 13 years old. She was treated as an inpatient at the St. Petersburg State Budgetary Healthcare Institution “Children's Infectious Diseases Hospital No. 3” in 2023 with the diagnosis “Right-sided exudative pleurisy of tuberculous etiology, MBT (–)”. Allergological anamnesis was calm. She was treated according to III chemotherapy regimen with a standard set of first-line antituberculosis drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). At the start of tuberculosis chemotherapy, there were no clinical and laboratory manifestations of allergy, as well as liver function abnormalities. One month after the start of anti-tuberculosis chemotherapy, the appearance of eosinophilia up to 10% (650 cells in 1 μl) in the clinical blood test (initial index 3% (195 cells in 1 μl)) was noted during routine control examination. Simultaneously blood biochemical analysis showed an increase of ALT up to 227 units/l (more than 4 times higher than normal) and AST up to 292 units/l (more than 5 times higher than normal), which is an indication for cancellation of antituberculosis treatment.TB drugs were cancelled, detoxification therapy, antihistamine therapy, sorbents were prescribed to the child. A basophil activation test was performed, which was positive for two anti-TB drugs. The basophil activation index for isoniazid was 1.4 (N 0-1.1), basophil activation index for ethambutol 3.6 (N 0-1.1). Basophil activation index was negative for the rest of the drugs. According to the results of the research, the culprits that caused toxic-allergic reactions were identified, and chemotherapy was resumed by replacing ethambutol with amikacin. It was decided to preserve isoniazid since it was highly important in the treatment regimen. The antibiotic therapy was covered by courses of desensitizing therapy. The course of anti-tuberculosis therapy ended effectively with the clinical recovery of the child.

CASE HISTORY 2

A girl Ch., 4 years old. She was hospitalized at the St. Petersburg State Budgetary Healthcare Institution “Children's Infectious Diseases Hospital No. 3” in 2023 with the diagnosis “Tuberculosis of intrathoracic lymph nodes of the bronchopulmonary group on the left side in the phase of incomplete calcification, MBT (–)”. The patient had a allergic reactions to nuts, which manifested as skin rash and itching. There were no allergic

manifestations at the time of admission to the hospital. She underwent a standard examination by specialists, including an ophthalmologist; no visual disturbances were detected. She was treated according to the III regime of chemotherapy (isoniazid, rifampicin, ethambutol, pyrazinamide). One month after the start of treatment, the clinical blood test showed 9% (450 cells in 1 μl) eosinophils, other parameters were normal. Biochemical blood test showed ALT up to 69 units/l (slight increase) and AST up to 51 units/l (upper limit of norm). The child was tested for all TB drugs taken. A positive result was obtained for two drugs: basophil activation index for rifampicin 1.4 (N 0-1.1), basophil activation index for ethambutol 2.0 (N 0-1.1). At the same time ophthalmologist revealed a typical toxic reaction to ethambutol in the form of impaired color perception. Taking into account high sensitization to ethambutol in combination with its characteristic toxic effect on vision, this undesirable adverse reaction was considered as toxic-allergic effect of ethambutol. The drug was cancelled for the whole period of treatment. Taking into account the positive BAT for rifampicin, hepatoprotective therapy and courses of antihistamines were intensified, and its use was continued. Further treatment was completed successfully without UARs.

Thus, the high-tech basophil activation test is a minimally invasive, safe, informative method in determining undesirable adverse reactions by detecting hidden sensitization to antituberculosis drugs. It allows to effectively predict undesirable adverse reactions and identify the culprit drug. The use of minimally invasive and safe diagnostic methods is especially relevant in pediatric practice. Such laboratory diagnostics is available for any specialists, it does not require a large number of additional laboratory and instrumental studies.

Comprehensive diagnosis of allergic conditions, including the use of pathogenetically determined laboratory methods, will contribute to adequate treatment and, consequently, to the improvement of public health.

CONCLUSION

1. A cohort retrospective study including 146 children undergoing the intensive phase of tuberculosis chemotherapy in 2018–2021 found that undesirable adverse reactions with an allergic component were observed in 37.0% of children, including allergic ones in 21.9% of children and toxic-allergic ones in 15.1% of patients.

2. The basophil activation test makes it possible to determine sensitization to the main TB drugs. Allergic and toxic-allergic reactions were most often sensitized to rifampicin (35.3%) and ethambutol (42.9%). In toxic reactions, sensitization to pyrazinamide was more common (46.2%).

3. Calculation of the odds ratio of allergic and toxic-allergic reactions showed that a positive basophil activation test increases the chance of their occurrence by 85 times.

4. The basophil activation test has high sensitivity (94.4%) and specificity (at least 83.3%), it is a valuable and promising method of determining the sensitization to antituberculosis drugs, allowing to prevent the development of undesirable adverse reactions caused by allergy. It is particularly useful in difficult cases when there is poor tolerance to chemotherapy and it is hard to identify the culprit drug causing undesirable adverse reactions.

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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ASSESSMENT AND SELF-ASSESSMENT OF PHYSICAL DEVELOPMENT IN HIGH SCHOOLCHILDREN IN THE REPUBLIC OF TUVA

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ABSTRACT. ***Introduction.*** Research conducted in recent years indicates negative trends in physical development indicators of the country's younger generation, but there is not enough data on the growth and development of children and adolescents in the Republic of Tyva. ***The purpose of the study*** is to assess physical development and the objectivity of its perception by adolescents of the titular nationality of Tyva. ***Materials and methods.*** The study involved 509 schoolchildren aged 15–17 years who permanently reside in the capital (Kyzyl) and settlements in the regions (kozhuuns Baryyn-Khemchik, Bii-Khem, Mongun-Taiga, Tandy and Kyzyl) of the republic. The study included an assessment of the level of physical development, characteristics of nutritional status according to the standards of "WHO Growth Reference 2007", Self-assessment survey of body weight and body composition. ***Results.*** It was revealed that in 71.1–73.6% of adolescents, standing height indicators corresponded to average values. Height above average was less common (7.5–9.5%) than height below average (16.9–21.4%). Correspondence of body weight to its length was registered in 64.4–72.9% of schoolchildren; girls more often than boys (p=0.04). Underweight was detected more often (18.0–19.1%) than overweight (9.1–16.5%). Overweight and obesity were more often identified in boys than girls (p=0.006). ***Conclusion.*** Self-assessment of physical development by schoolchildren differs significantly from the objective status. Girls are more often dissatisfied with their weight and physique than boys. Behavior aimed at weight correction is more typical for girls (especially those living in the city).

KEYWORDS: *schoolchildren, adolescents, physical development, nutritional status, indigenous population, Republic of Tyva*

ОЦЕНКА И САМООЦЕНКА ФИЗИЧЕСКОГО РАЗВИТИЯ У СТАРШИХ ШКОЛЬНИКОВ В РЕСПУБЛИКЕ ТЫВА

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РЕЗЮМЕ. ***Введение.*** Проведенные в последние годы исследования свидетельствуют о негативных тенденциях показателей физического развития подрастающего поколения страны, однако данных о росте и развитии детей и подростков в Республике Тыва недостаточно. ***Цель исследования*** — дать оценку физического развития и объективности его восприятия подростками титульной национальности Тывы. ***Материалы и методы.*** В исследовании приняли участие 509 школьников в возрасте 15–17 лет, которые постоянно проживают в столице (г. Кызыл) и населенных пунктах в районах (кожуунах Барыын-Хемчик, Бии-Хем, Монгун-Тайга, Таңды и Кызыл) республики. Исследование включало оценку уровня физического развития, характеристику нутритивного статуса по нормативам WHO Growth Reference 2007, анкетирование по самооценке массы тела и телосложения. ***Результаты.*** Выявлено, что у 71,1–73,6% подростков показатели роста стоя соответствовали средним значениям. Рост выше средних значений встречался реже (7,5–9,5%), чем рост ниже среднего (16,9–21,4%). Соответствие массы тела его длине зарегистрировано у 64,4–72,9% школьников; у девушек чаще, чем у юношей (p=0,04). Дефицит массы тела выявлялся чаще (18,0–19,1%), чем повышенная масса тела (9,1–16,5%). Избыточная масса тела и ожирение чаще определялись у юношей, чем у девушек (p=0,006). ***Заключение.*** Самооценка физического развития школьниками существенно отличается от объективного статуса. Чаще неудовлетворены своим весом и телосложением девушки, чем юноши. Поведение, направленное на коррекцию веса, в большей степени характерно для девушек (особенно проживающих в городе).

КЛЮЧЕВЫЕ СЛОВА: *школьники, подростки, физическое развитие, нутритивный статус, коренное население, Республика Тыва*

INTRODUCTION

Health state of the younger generation is one of the benchmarks of socio-economic well-being of both a particular region and the state as a whole [1, 2]. Simplicity, accessibility and high informativeness of physical development indicators allow their use in socio-hygienic and territorial-environmental monitoring of the health of children and adolescents [3, 4]. The data published in recent years indicate numerous deviations in the physical and reproductive health of adolescents, which creates a certain risk for the demographic and economic well-being of the country [5, 6].

The Republic of Tyva (RT) is a region of the Russian Federation characterized by a significant dominance of representatives of the titular nationality — Tuvinians. The demographic situation in the republic is also characterized by high birth rates, mortality, migration and low urbanization [7, 8]. Earlier studies in Tyva have revealed the peculiarities of growth, development and nutrition of schoolchildren [9–12]. However, these data need to be supplemented in accordance with modern international methods and trends, which became the prerequisite for our research.

AIM

To assess the physical development and objectivity of its perception by adolescents of the Tyva titular nationality.

MATERIALS AND METHODS

509 adolescents aged 15–17 years participated in the research after signing informed consent. They were students of public schools of Kyzyl, the capital of Tyva, as well as settlements in the Bariyn-Khemchik, Bii-Khem, Mongun-Taiga, Tanndy, and Kyzyl kyuons. All adolescents surveyed were ethnic Tuvinians, descended from mono-ethnic marriages. The group of urban schoolchildren comprised 151 girls and 105 boys, while 133 girls and 120 boys were examined in the districts of the republic (kojuns). The research included somatometry (height and body weight) and interviewing with the help of a specially designed questionnaire. A standardized anthropometric method of V.V. Bunak (1941) was used. The requirements of the Research Institute of Anthropology of Moscow State University (1982) were taken into account, and medical equipment that had passed metrological verification was used.

Physical development (PD) was assessed according to the World Health Organization (WHO) Growth Reference 2007 by means of WHO AnthroPlus program (anthropometric calculator) [13, 14]. The PD level was characterized by comparing individual height indices with age-sex norms. Depending on the number of standard deviations (SD) that distinguish the student's height value from the median index, the following variants of PD were identified: “average” (APD; ±1SD); “above average” (AAPD; from +1SD to +2SD); “high” (HPD; more than +2SD); “below average” (BAPD; from –1SD to -2SD); “low” (LPD; less than –2SD).

Nutritional status was assessed by Kettle's body mass index (BMI), the value of which was determined by dividing body weight (kg) by the square of height (m^2). The following variants were identified in accordance with the compliance of BMI and centile scale norms: harmonious ratio of body weight and length (HPD; 15th-85th percentile), malnutrition (MN; 5th–15th percentile), undernutrition (UN; below the 5th percentile), overweight (OW; 85th–95th percentile); obesity (Ob) was registered when BMI value exceeded the 95th percentile.

During interviewing, schoolchildren were asked to characterize their body, express the degree of satisfaction with their weight and body shape; to note the use of diet and/or other ways to regulate body weight.

Statistical processing of the study material was carried out by methods of variation statistics using STATISTICA v.10.0 (StatSoft, USA). The obtained indices are presented as P [CI]%, where P is the percentage, CI is the 95% confidence interval for the percentage. Significance of intergroup differences in traits was performed using Pearson's χ^2 test (with Yates correction). Differences in results were considered statistically significant at $p < 0.05$.

RESULTS

One of leading indicators of PD is the compliance of standing height with the norms of age-sex scale. 73.6% [71.0–76.2] of girls and 71.1% [68.2–74.1] of boys

showed HPD. Above-average height was less common (8.4% [6.8–10.0] of girls and 7.1% [5.4–8.8] of boys) than below-average height (15.1% [13.0–17.2] and 14.7% [12.4–17.0], respectively). Stunting requiring further clinical examination was more frequently reported in boys (6.7% [5.1–8.3]) than in girls (1.8% [1.0–2.6]; p=0.005). There were fewer schoolchildren with high stature: 1.1% [0.5–1.7] of girls and 0.4% [0.1–0.7] of boys. Distribution by PD level of senior schoolchildren living in urban and rural areas is presented in Figure 1. A statistically significant difference of indicators depending on the place of residence was revealed in boys with APD (p=0.002) and LPD (p=0.03). Whereas girls' indicators did not differ significantly.

The majority of participants had body weight that matched their standing height. Girls were more likely to have this match (72.9% [70.3–75.5]) than boys (64.4% [61.2–67.6]; p=0.04). Disharmonic variants of PD due to body weight deficiency were detected more frequently (18.0–19.1%) than those associated with increased weight (9.1-16.5%). The incidence of MN (2.7% [1.6–3.8]) and obesity (4.5% [3.1–5.9]; p=0.006) was higher in boys than in girls (1.9% [1.1–2.7] and 0.8% [0.2–1.2], respectively). The distribution of high school students by the degree of nutritional status, taking into account the level of urbanization of their place of residence, is presented in Figure 2. HPD was more common in urban schoolchildren, but statistically significant difference of indicators was found only in urban residents (p=0.04). Malnutrition was more frequently revealed in urban high school children than in their rural peers, but the difference of indicators is not statistically significant. Undernutrition was registered equally often among urban and rural boys, but there were more girls with undernutrition in kojuns than among urban peers (p=0.02). Excessive body weight was more frequently registered in boys than in girls, but the difference was statistically insignificant. BMI indicators corresponding to obesity were found more often in the group of urban adolescents (p=0.007).

The objectivity of adolescents' perception of their body is very important for dietary control, prevention/correction of deviant forms of eating behavior [15–18]. Distribution of participants by perception of their body is presented in Table 1. The majority of schoolchildren thought that their body was normal, boys more often assessed their body as normal than girls (p=0.01-0.0008), rural adolescents more often than their urban peers (p=0.0002). Schoolchildren considered their body to be overweight more often (24.7–12.5%) than thin (10.2–12.4%), which was more typical for girls than for boys (p=0.04–0.002). Only females considered themselves as obese, even though obesity was reported more frequently in males.

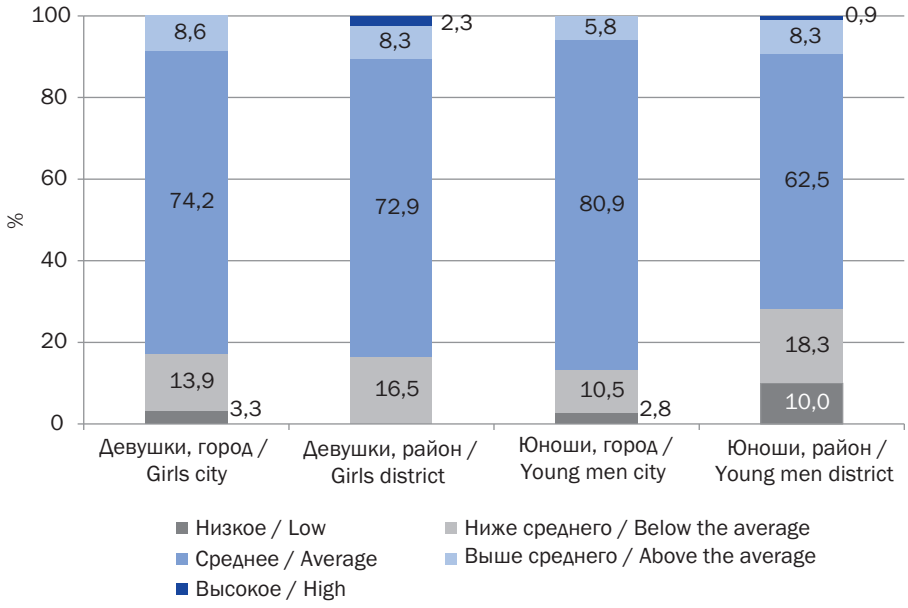

Fig. 1. Characteristics of the level of physical development of adolescents (% [95% CI])

Рис. 1. Характеристика уровня физического развития подростков (% [95% ДИ])

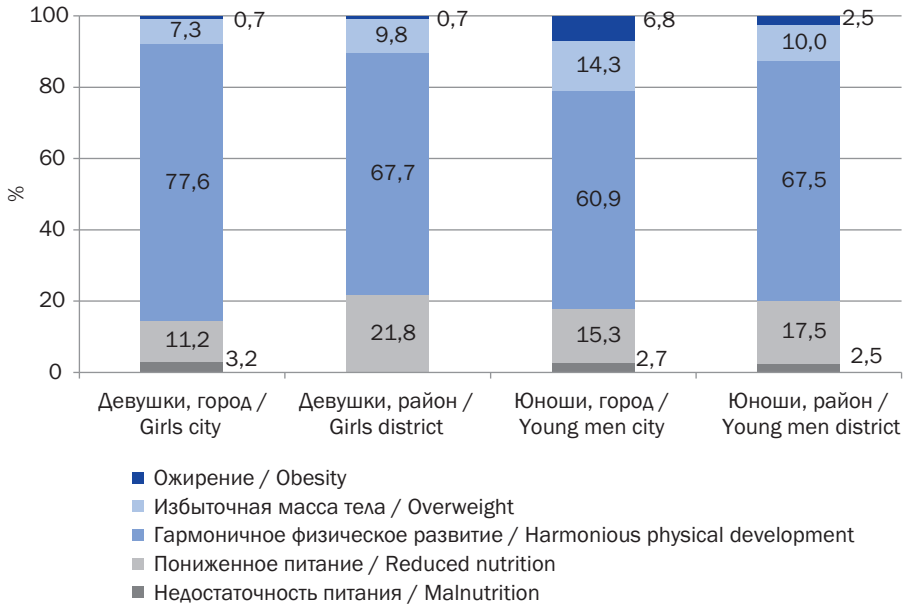

Fig. 2. Characteristics of the nutritional status of adolescents (% [95% CI])

Рис. 2. Характеристика нутритивного статуса подростков (% [95% ДИ])

Table 1. Distribution of schoolchildren according to their body perception options (% [95% CI])

Таблица 1. Распределение школьников по вариантам восприятия своего тела (% [95% ДИ])

Группа / Group		Восприятие своего тела / Perception of your body				
		очень худое / very thin	худое / thin	нормальное / normal	полное / portly	очень полное / very portly
Девушки / Girls	1. Город / City n=151	1,3 [0,4–2,2]	7,9 [5,7–10,1]	63,6 [59,7–67,5]	26,5 [22,9–30,1]	0,7 [0,1–1,2]
	2. Район / District n=133	0	11,3 [8,6–14,0]	66,9 [62,7–70,8]	18,8 [15,4–22,2]	3,0 [1,6–4,5]
	3. Всего / Total n=284	0,7 [0,2–1,1]	9,5 [7,8–11,2]	65,1 [62,3–67,9]	22,9 [20,5–25,3]	1,8 [1,0–2,6]
Юноши / Young men	4. Город / City n=105	7,6 [5,0–10,2]	12,4 [9,2–15,6]	63,8 [59,2–68,4]	16,2 [12,6–19,8]	0
	5. Район / District n=120	0	5,8 [3,7–7,9]	85,0 [81,8–88,2]	9,2 [6,6–11,8]	0
	6. Всего / Total n=225	3,5 [2,3–4,7]	8,9 [7,0–10,8]	75,1 [72,3–77,9]	12,5 [10,3–14,7]	0
Примечание / Note		P_{1-4}=0,01; P_{4-5}=0,002; P_{3-6}=0,02		P_{2-5}=0,0008; P_{4-5}=0,0002; P_{3-6}=0,01	P_{1-4}=0,05; P_{2-5}=0,03; P_{3-6}=0,002	P_{2-5}=0,05; P_{3-6}=0,04

Table 2 presents the results of schoolchildren's satisfaction with their body weight. Boys are more often satisfied with their body weight than girls (p=0.02), and this is more pronounced in adolescents living in kojuns (p=0.004). 1/3 of respondents have a neutral attitude to their weight, no difference in indicators depending on gender and place of residence was revealed. Girls expressed dissatisfaction with their body weight more often than their male peers (p=0.01); schoolgirls from rural areas are dissatisfied to a greater extent (p=0.001). Boys from urban areas were more often very dissatisfied with body weight among, whereas in rural areas girls were more often dissatisfied with body weight than their male peers;

Table 2. Distribution of schoolchildren by satisfaction with their body weight (% [95% CI])

Таблица 2. Распределение школьников по удовлетворенности массой своего тела (% [95% ДИ])

Группа / Group		Отношение к массе своего тела / Attitude towards your body weight			
		доволен / happy	нейтральное отношение / neutral attitude	недоволен / dissatisfied	очень недоволен / very dissatisfied
Девушки / Girls	1. Город / City n=151	31,8 [28,0–35,6]	45,0 [41,1–48,9]	21,8 [18,5–25,1]	1,4 [0,5–2,3]
	2. Район / District n=133	24,1 [20,4–27,8]	41,3 [37,1–45,5]	30,8 [25,9–34,7]	3,8 [2,2–5,4]
	3. Всего / Total n=284	28,2 [25,5–30,9]	43,3 [40,4–46,2]	26,0 [23,4–28,6]	2,5 [1,7–3,3]
Юноши / Young men	4. Город / City n=105	35,2 [30,6–39,8]	40,9 [36,1–45,7]	20,8 [16,9–24,7]	3,1 [1,4–4,8]
	5. Район / District n=120	40,8 [36,3–45,3]	44,2 [39,7–48,8]	13,3 [10,2–16,4]	1,7 [0,5–2,9]
	6. Всего / Total n=225	38,2 [35,0–41,4]	42,7 [39,4–46,0]	16,9 [14,4–19,4]	2,2 [1,3–3,1]
Примечание / Note		P_{2-5}=0,004; P_{3-6}=0,02		P_{2-5}=0,001; P_{3-6}=0,01	

Table 3. Distribution of schoolchildren's satisfaction with their body shape (% [95% CI])

Таблица 3. Распределение школьников удовлетворенности формой своего тела (% [95% ДИ])

Группа / Group		Отношение к форме тела / attitude towards the shape of body			
		доволен / happy	нейтральное отношение / neutral attitude	недоволен / dissatisfied	очень недоволен / very dissatisfied
Девушки / Girls	1. Город / City n=151	36,4 [32,5–40,3]	41,0 [37,1–44,9]	21,2 [17,8–24,6]	1,4 [0,5–2,3]
	2. Район / District n=133	25,6 [21,8–29,4]	48,9 [44,6–53,2]	21,8 [18,2–25,4]	3,7 [2,1–5,3]
	3. Всего / Total n=284	31,3 [28,6–34,0]	44,7 [41,8–47,6]	21,5 [19,1–23,9]	2,5 [1,6–3,4]
Юноши / Young men	4. Город / City n=105	32,4 [27,9–36,9]	46,7 [41,9–51,5]	18,1 [14,4–21,8]	2,8 [1,1–4,5]
	5. Район / District n=120	25,8 [21,9–29,7]	53,3 [48,9–57,8]	16,7 [13,3–20,1]	4,2 [2,4–6,0]
	6. Всего / Total n=225	28,9 [25,8–31,7]	50,2 [46,9–53,5]	17,3 [14,8–19,7]	3,6 [2,4–4,8]
Примечание / Note		P_{1-2}=0,05			

however, the difference of indicators is not statistically significant.

The distribution of respondents depending on satisfaction with their body shape is presented in Table 3. 1/3 of schoolchildren are satisfied with their body shape. Urban teenagers are more often satisfied with their body shape than those living in villages. Boys are more often than girls have both neutral and extremely negative attitude to body shape. Among those dissatisfied with body shape there are more girls than boys, but the difference is not statistically significant.

Interviews clarified their attitude to weight correction and the use of corrective methods in practice; the data are presented in Table 4. Behavior aimed at weight correction is more typical for girls than boys (p=0.0000), and for urban schoolgirls compared to their peers living in rural areas (p=0.006). They believe that body weight does not need correction, so they do not

Table 4. Distribution of schoolchildren by options for body weight correction (% [95% CI])

Таблица 4. Распределение школьников по вариантам коррекции массы тела (% [95% ДИ])

Группа / Group		Соблюдение диеты или других методов по коррекции массы тела / following a diet or other methods to correct body weight			
		нет, вес нормальный / no, normal weight	нет, но хочу снизить вес / no, but I want to lose weight	нет, но хочу повысить вес / no, but I want to gain weight	да, применяю / yes, I do
Девушки / Girls	1. Город / City n=151	46,3 [42,4–50,2]	27,1 [23,5–30,7]	4,6 [2,9–6,3]	22,0 [18,6–25,4]
	2. Район / District n=133	45,9 [41,6–50,2]	32,3 [28,4–36,2]	12,0 [9,2–14,8]	9,8 [7,2–12,4]
	3. Всего / Total n=284	46,1 [43,2–49,0]	29,5 [26,8–32,2]	8,1 [6,5–9,7]	16,3 [14,1–18,5]
Юноши / Young men	4. Город / City n=105	57,1 [52,4–61,9]	20,0 [16,1–23,9]	18,1 [14,4–21,8]	4,8 [2,7–6,9]
	5. Район / District n=120	61,7 [57,3–66,1]	20,0 [16,4–23,6]	14,2 [11,0–17,4]	4,1 [2,3–5,9]
	6. Всего / Total n=225	59,5 [56,3–62,7]	20,0 [17,3–22,7]	16,0 [13,6–18,4]	4,5 [3,1–5,9]
Примечание / Note		P_{2-5}=0,01; P_{3-6}=0,002	P_{2-5}=0,03; P_{3-6}=0,01	P_{1-2}=0,02; P_{1-4}=0,0004; P_{3-6}=0,006	P_{1-2}=0,006; P_{1-4}=0,0001; P_{3-6}=0,0000

follow a diet and/or do not increase physical activity. It is more common among boys than girls (p=0.002). Girls would like to reduce their body weight but do not make efforts to do so more often than boys (p=0.01). Boys (p=0.006) and girls from rural areas (p=0.02) wanted to increase their body weight but did not use any correction methods more often than urban girls.

CONCLUSION

The structure of PD level in the examined schoolchildren shows that the majority (62.5-80.9%) have height indices that correspond to the average values of international norms. At the same time, it should be noted that the proportion of adolescents with below-average height (16.9-21.4%) exceeds the proportion of peers with above-average height (7.5–9.5%), which may be due to both ethnic constitutional features and the influence of environmental factors. This circumstance creates prerequisites for further advanced research.

Regional peculiarities of nutritional status were revealed as well: a share of pupils with body weight deficiency is rather high (11.2–21.8%). The data coincide with the results of a study of schoolchildren in Erzin kojun (11–27%) [19]. Other studies in schoolchildren of the Mongoloid race in the Republic of Tyva (Toora-Khem village, Toju kojun) and the Republic of Sakha (Yakutia) reported a much lower proportion of underweight adolescents (1.9–3.9%) [20, 21]. In total, the proportion of overweight and obese adolescents in our study is lower (9.1–16.5%) than in Tozhu and Erzin (13.5–17.6%) [19, 20]. It is necessary to analyze actual nutrition of adolescents in detail to clarify the causes of disharmonious physical development.

Schoolchildren's self-assessment of physical development differs significantly from our objective characterization. Girls (28.5%) are more often dissatisfied with their weight and body shape than their male peers (19.1%). Girls are more frequently engaged in weight correction (16.3%; especially those living in the city — 22%) than boys (4.5%). It should be noted that the overall proportion of schoolchildren controlling their weight through diet and/or physical activity is lower than the proportion of students at Tuva State University [22]. Our results correspond with the data of other authors, which also indicate that the proportion of adolescents taking measures of weight correction is lower than the WHO recommendation [23, 24].

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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INFLUENCE OF OVERWEIGHT AND OBESITY ON REVERSIBILITY OF BRONCHIAL OBSTRUCTION IN CHILDREN WITH BRONCHIAL ASTHMA

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ABSTRACT. ***Introduction.*** Most modern publications report the formation of an obstructive pattern of external respiration in children with a combination of bronchial asthma (BA) and obesity, including due to the formation of dysanapsis in them. However, data on the effect of overweight and obesity on the reversibility of bronchial obstruction in patients with BA and obesity are rare and contradictory. ***The aim of the study*** was to study the effect of overweight and obesity on the reversibility of bronchial obstruction in children and adolescents with asthma. ***Materials and methods.*** A single-center observational cross-sectional pilot study was conducted. 161 patients with asthma aged from 8 to 17 years were examined. Anthropometric and spirometric parameters were measured, z body mass index (BMI), WC (waist circumference)/height, bronchodilation coefficient (BDC) were calculated. The study participants were divided into two groups: group 1 — with normal body weight (BW), group 2 — with overweight, obesity. ***Results.*** BDC was statistically significantly lower in the group with overweight, obesity, amounting to 5.57 [1.07; 9.16]% versus 10.20 [3.67; 17.94]%, p <0.001. BDC was statistically significantly lower in the group with abdominal type of obesity, amounting to 5.83 [1.07; 9.16]% versus 7.67 [3.67; 13.76]%, p=0.034. Negative correlations were found between BDC and z BMI, WC/height, R=−0.29, p=0.0002, R=−0.31, p=0.004, respectively. ***Conclusions.*** In patients with BA and overweight, obesity, the reversibility of bronchial obstruction in tests with bronchodilators is lower than in patients with normal BW. This may reflect the formation of a fixed obstruction component in overweight and obese patients.

KEYWORDS: *bronchial asthma, obesity, overweight, spirometry, children*

ВЛИЯНИЕ ИЗБЫТОЧНОЙ МАССЫ ТЕЛА И ОЖИРЕНИЯ НА ОБРАТИМОСТЬ БРОНХИАЛЬНОЙ ОБСТРУКЦИИ У ДЕТЕЙ С БРОНХИАЛЬНОЙ АСТМОЙ

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РЕЗЮМЕ. ***Введение.*** В большинстве современных публикаций сообщается о формировании обструктивного паттерна внешнего дыхания у детей с сочетанием бронхиальной астмы (БА) и ожирения, в том числе вследствие формирования у них дисанапсиса. Однако данные о влиянии избыточной массы тела, ожирения на обратимость бронхиальной обструкции у пациентов с БА и ожирением единичны и противоречивы. ***Цель исследования —*** изучить влияние избыточной массы тела, ожирения на обратимость бронхиальной обструкции у детей и подростков с БА. ***Материалы и методы.*** Было проведено одноцентровое наблюдательное поперечное пилотное исследование. Обследован 161 пациент с БА в возрасте от 8 до 17 лет. Проведено измерение антропометрических и спирометрических показателей, рассчитаны z индекса массы тела (ИМТ), ОЖ (окружность живота)/рост, коэффициент бронходилатации (БДК). Участники исследования разделены на две группы: 1-я группа — с нормальной массой тела (МТ), 2-я группа — с избыточной МТ и ожирением. ***Результаты.*** БДК был статистически значимо ниже в группе с избыточной МТ, ожирением, составив 5,57 [1,07; 9,16]% против 10,20 [3,67; 17,94]%, p <0,001. БДК был статистически значимо ниже в группе с абдоминальным типом ожирения, составив 5,83 [1,07; 9,16]% против 7,67 [3,67; 13,76]%, p=0,034. Выявлены отрицательные корреляционные взаимосвязи между БДК и z ИМТ, ОЖ/рост, R= −0,29, p=0,0002, R= −0,31, p=0,004, соответственно. ***Выводы.*** У пациентов с БА и избыточной МТ, ожирением обратимость бронхиальной обструкции в тестах с бронхолитиками ниже, чем у пациентов с нормальной МТ. Это может отражать формирование фиксированного компонента обструкции у пациентов с избыточной МТ и ожирением.

КЛЮЧЕВЫЕ СЛОВА: *бронхиальная астма, ожирение, избыточная масса тела, спирометрия, дети*

INTRODUCTION

Overweight and obesity contribute to negative modifications in bronchial asthma (BA) and exacerbate its course. BA phenotype in combination with obesity is complex. It is not fully understood in children and adolescents [1–3]. Most modern publications report the formation of obstructive pattern of external respiration in children and adolescents with a combination of BA and obesity, including the formation of dysanapsis [4–9].

At the same time, there are few and contradictory data on reversibility of bronchial obstruction in overweight and obese patients with BA. J.A. Castro-Rodríguez et al. demonstrated that girls who became overweight or obese between the ages of 6 and 11 years were more likely to demonstrate reversibility of bronchial obstruction than girls who were not overweight or obese [10]. At the same time, K.G. Tansitira et al. reported that sensitivity to BD decreased with increasing body mass index (BMI) in obese children [11]. A.E. Dixon et al. performed a research in adults and found no association between obesity and reversibility of airway obstruction [12].

Thus, at present, the influence of obesity on the reversibility of bronchial obstruction in children and adolescents with the phenotype 'BA and obesity' cannot be considered ascertained.

AIM

To study the effect of overweight and obesity on the reversibility of bronchial obstruction in children and adolescents with bronchial asthma.

MATERIALS AND METHODS

Design. A single-center observational cross-sectional research was conducted.

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

Participants. The study included patients with atopic BA, they were 8 to 17 years old, and received treatment. Atopy-related family history (asthma, allergic rhinitis, conjunctivitis, atopic dermatitis, urticaria) was assessed. Sensitization to major aeroallergens (house dust mite, cat, dog, pollen allergens) was tested by *in vivo* (prick tests) or *in vitro* (with determination of specific IgE) methods [13].

Inclusion criteria for the research were:

1) diagnosis of BA established according to current international consensus documents (GINA, 2016–2024) [1];
2) age of patients between 8 and 17 years.

Non-inclusion criteria were:

1) patients with a BMI greater than +2.5Z;
2) presence of acute infectious diseases and fever;
3) presence of diabetes mellitus, autoimmune disorders, primary immunodeficiencies, oncological diseases, atopic dermatitis, parasitic diseases;
4) severe course of BA [1];
5) systemic use of glucocorticoids;
6) use of non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors used for epilepsy.

Ethical review

The study was approved by the Ethical Committee of the Volga Region Research Medical University (protocol No. 8 dated 27.05.2022). All participants and all primary caregivers gave their written informed consent.

Data sources

Anthropometric indices. All patients were assessed for basic anthropometric indices. All measurements were performed without shoes, outer clothing and headwear. Anthropometric parameters (height, body weight and BMI) were estimated using the tables developed by WHO, taking into account sex and age of patients (https://www.who.int/tools/child-growth-standards).

1. BMI calculation:

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

According to BMI estimation, children were divided into two groups:

- Group 1 — normal body weight (BMI values from –1Z to +1Z);
- Group 2 — overweight and obese (BMI values above +1Z but not more than +2.5Z).

2. Measurement of abdominal circumference (AC) was performed. Measurements were taken at the end

of normal exhalation using a flexible tape, at equidistant circumference between the upper border of the iliac crest and the lower edge of the rib. Abdominal obesity was assumed if the AC exceeded the 90th percentile [14, 15].

3. The ratio of abdominal circumference to height was calculated using the formula:

AC / height = Abdominal circumference / Height.

Spirometry. Spirometry studies were performed with Mastercreen pneumospirometer (Jaeger, Germany). When analyzing spirometry data, the following parameters were evaluated:

- FVC (l) — forced vital capacity of the lungs, reflects the lung volume;
- FEV_1 (l/s) — forced expiratory volume in 1 second;
- FEV_1/FVC — index serving as the main parameter of spirometry for diagnostics of obstructive disorders.

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

Bronchodilation coefficient (BDC) was calculated according to the formula [16]:

$$BDC = \frac{\text{Index after bronchodilator, l} - \text{Index before bronchodilator, l}}{\text{Index before bronchodilator, l}} \cdot 100\%.$$

In addition, z FEV_1/FVC was calculated using the Global Lung Function Initiative calculator (http://gli-calculator.ersnet.org/index.html), created with the support of the European Respiratory Society (ERS, https://www.ersnet.org).

Statistical analysis. Statistical analysis was performed using Statgraphics Centurion v.16. Quantitative indicators were evaluated for conformity to normal distribution, for this purpose the Shapiro-Wilk criterion was used (when the number of subjects was less than 50) or the Kolmogorov–Smirnov criterion (when the number of subjects was more than 50), as well as the asymmetry and excess indices. Data are presented as Me [Q1; Q3], where Me — median, [Q1; Q3] — 1st and 3rd quartiles in case distribution differs from a normal distribution. The Mann-Whitney test was used to compare quantitative variables in two independent groups. Differences between two dependent groups were determined using Wilcoxon's W-criterion. Correlation analyses were performed for normally distributed variables using Pearson's correlation coefficient, and for non-normally distributed variables using Spearman's rank correlation coefficient. Categorical data were described with absolute values and percentages. Differences were assessed using Pearson's χ^2 criterion. If the number of expected observations in any of the cells of the four-field table was less than 10, Fisher's exact test was used to assess the significance level of differences. Differences were considered statistically significant at $p < 0.05$.

The study was a pilot trial, so no sample size calculation was performed. Inclusion was restricted to those patients who had no omissions in the examinations performed.

RESULTS

Patients with 'normal body weight' and 'overweight/obesity' were compared by gender and age (Table 1). The parameters z Height, z BMI were statistically significantly higher in patients who were overweight

Table 1. Clinical characteristics of patients

Таблица 1. Клиническая характеристика пациентов

Параметры / Parameters	Все пациенты / All patients (N=161)	Нормальная масса тела / Normal body weight (N=92)	Избыточная масса тела и ожирение / Overweight and obese (N=69)	Значение p / p-value
Возраст, лет / Age, years	11,0 [9,0; 14,0]	10,0 [8,0; 14,0]	12,0 [9,0; 14,0]	0,498
Мальчики, n=66 / Boys, n=66	74,5% (120/161)	77,2% (71/92)	71,0% (49/69)	0,682
z Роста / z Height	0,73 [0,06; 1,60]	0,41 [-0,10; 1,16]	1,20 [0,56; 1,81]	<0,001
z ИМТ / z BMI	0,75 [–0,07; 1,40]	0,15 [–0,39; 0,55]	1,54 [1,23; 2,10]	<0,001

Ending of the Table 1 / Окончание табл. 1

Параметры / Parameters	Все пациенты / All patients (N=161)	Нормальная масса тела / Normal body weight (N=92)	Избыточная масса тела и ожирение / Overweight and obese (N=69)	Значение p / p-value
ОЖ перц / WC perc	78,0 [70,0; 95,0]	72,0 [67,0; 78,0]	85,0 [81,0; 97,0]	<0,001
ОЖ/рост / WC/height	0,48 [0,44; 0,53]	0,44 [0,42; 0,46]	0,53 [0,48; 0,56]	<0,001
z $ОФВ_1$/ФЖЕЛ / z FEV_1/FVC	–1,46 [–2,23; –0,62]	–1,32 [–2,23; –0,43]	–1,64 [–2,19; –0,88]	0,028
БДК, % / BDC, %	7,38 [2,51; 14,40]	10,20 [3,67; 17,94]	5,57 [1,07; 9,16]	<0,001

Note: BDC — bronchodilation coefficient; BMI — body mass index; AG — abdominal circumference; FEV_1 — forced expiratory volume in 1 second; FVC — forced vital capacity.

Примечание: БДК — коэффициент бронходилатации; ИМТ — индекс массы тела; ОЖ — окружность живота; $ОФВ_1$ — объем форсированного выдоха за 1 секунду; ФЖЕЛ — форсированная жизненная емкость легких.

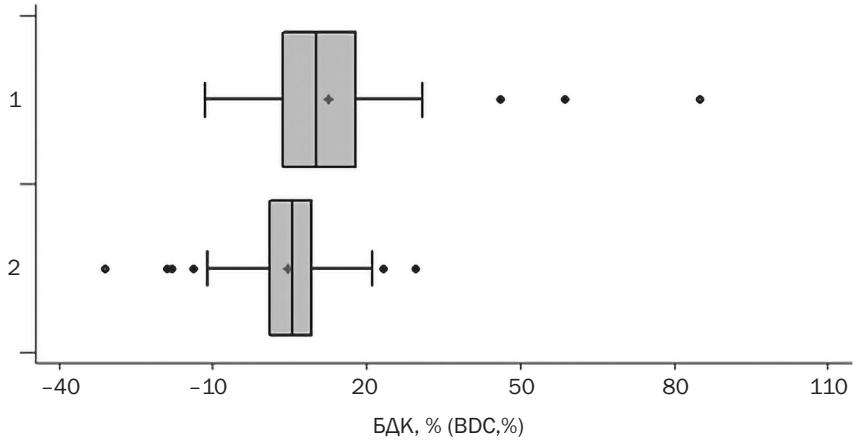

Fig. 1. Bronchodilation coefficient in children with asthma and different BMI (1 — normal body weight, 2 — overweight, obesity)

Рис. 1. Коэффициент бронходилатации у детей с бронхиальной астмой и различным ИМТ (1 — нормальная масса тела, 2 — избыточная масса тела, ожирение)

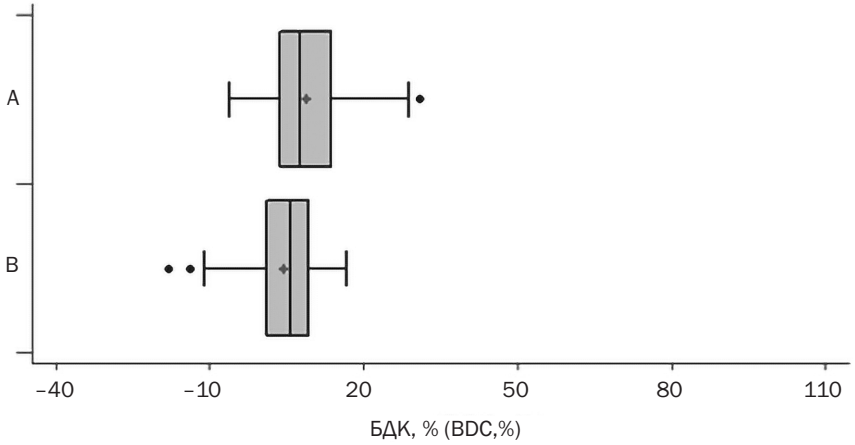

Fig. 2. The coefficient of bronchodilation in the groups: A — with the absence of abdominal type of obesity; B — with the presence of abdominal type of obesity

Рис. 2. Коэффициент бронходилатации в группах: А — с отсутствием абдоминального типа ожирения; В — с наличием абдоминального типа ожирения

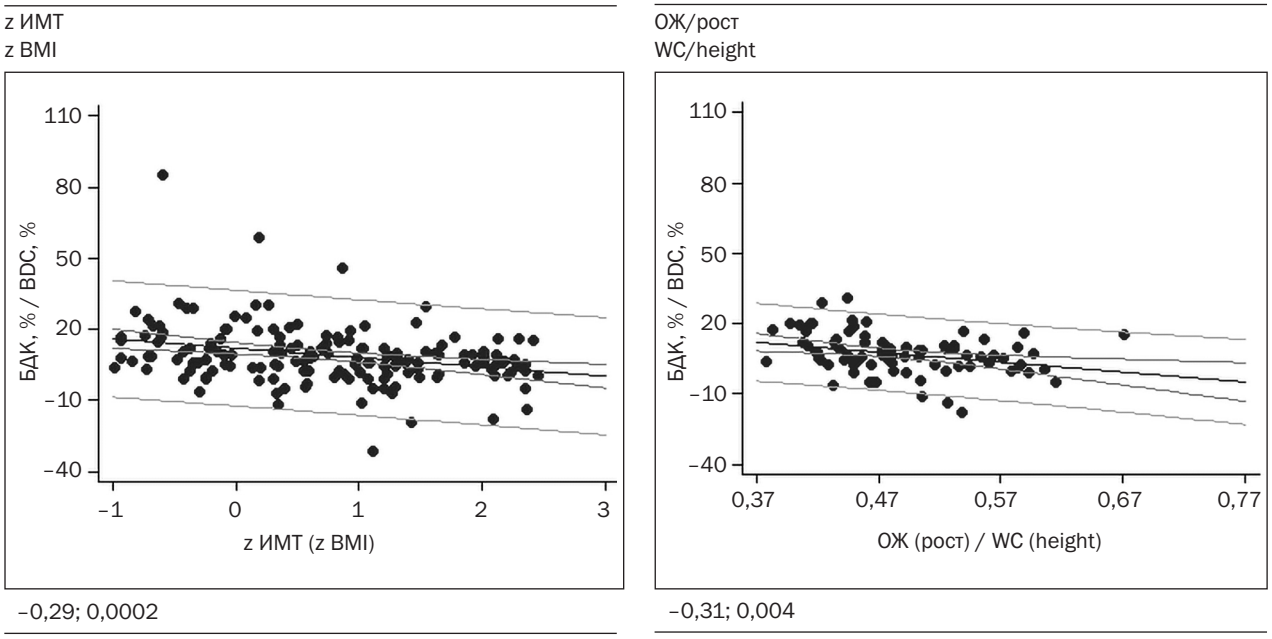

Fig. 3. Correlations between bronchodilation coefficient and z BMI, WC/height. The data is presented in the form of R, p, where R — the correlation coefficient, p — the level of statistical significance

Рис. 3. Корреляционные взаимосвязи между коэффициентом бронходилатации и z ИМТ, ОЖ/рост. Данные представлены в виде R, p, где R — коэффициент корреляции, p — уровень статистической значимости

and/or obese (p <0.05). The values of ACpertz, AC/growth were statistically significantly higher, and the parameters z FEV1/FVC were statistically significantly lower in the group of patients with overweight and obesity, all p <0.05. Bronchodilation ratio (BDR) was statistically significantly lower in the overweight and obese groups (p <0.001) (Fig. 1).

The bronchodilation ratio was statistically significantly lower in the group with abdominal type of obesity, being 5.83 [1.07; 9.16]% versus 7.67 [3.67; 13.76]%, p=0.034 (Fig. 2).

Negative correlations were found between bronchodilation ratio and z BMI, AC/height, R= −0.29, p=0.0002, R= −0.31, p=0.004, respectively (Fig. 3).

DISCUSSION

The current research focused on the effect of overweight and obesity, including abdominal obesity, on the reversibility of bronchial obstruction in spirometry tests with bronchodilators in children and adolescents with BA and overweight and obesity. Available researches devoted to abdominal type of obesity affecting the reversibility of obstruction have not been found.

The reversibility of bronchial obstruction in tests with bronchodilators in patients with the combination of BA with overweight and obesity appeared to be lower than in patients with normal body weight, being 5.57 [1.07; 9.16]% and 10.20 [3.67; 17.94]%, respectively, p <0.001. This may reflect the formation of a fixed component of obstruction in overweight and obese patients.

In addition to BMI, measurement of abdominal circumference, which is an anthropometric marker of the abdominal type of obesity, is a valuable anthropometric method for assessing obesity in children and adolescents. The bronchodilation ratio was statistically significantly lower in the group with abdominal type of obesity, being 5.83 [1.07; 9.16]% versus 7.67 [3.67; 13.76]%, p=0.034.

The results obtained correspond to the data of K.G. Tansitira et al. and Gonzalez-Uribe V. et al. [16, 17].

The mechanisms underlying the relationship between BMI and reversibility of bronchial airway obstruction in asthma continue to be investigated and possibly include a combination of factors, namely the effect of low-intensity systemic inflammation on changes in lung mechanics, airway structure, and susceptibility to BA.

The accumulation of adipose tissue in the airway walls of patients with BA and obesity is now considered an important potential mechanism for the changes in external respiration observed in obesity-related BA [18].

CONCLUSION

Therefore, patients with BA and overweight or obesity have a lower reversibility of bronchial obstruction in bronchodilator tests than patients with normal body weight. This may reflect the formation of a fixed component of obstruction in overweight and obese patients.

ADDITIONAL INFORMATION

The author' contribution to the work. Khramova R.N. — conceptualization, investigation, visualization, writing: review and editing.

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

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Informed consent to publication. The author received written consent from the legal representatives of the patients to publish medical data.

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Вклад автора в работу. Храмова Р.Н. — разработка концепции, проведение исследования, работа с данными, подготовка текста: оценка и редактирование.

Конфликт интересов. Автор заявляет об отсутствии конфликта интересов.

Источник финансирования. Автор заявляет об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Автор получил письменное согласие законных представителей пациентов на публикацию медицинских данных.

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FEATURES OF ORTHODONTIC TREATMENT OF CHILDREN WITH FOOD INTOLERANCE

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ABSTRACT. Food intolerance in childhood is manifested by various disorders on the part of the body when eating food. In this condition, there are violations of the work of many organs and systems in the body and the problem affects not only the work of the gastrointestinal tract, as well as other life-support systems of the body. With such disorders, metabolism and metabolic processes change. It is important for dentists to understand this problem, since the disease alters the local status localis in the oral cavity, which is the initial department of the gastrointestinal tract. This is expressed in a change in the physico-chemical properties of the oral fluid, causes dryness, a burning sensation on the part of the mucous membranes of the oral cavity. In the orthodontic treatment of such patients, it is necessary to carefully approach the issues of manufacturing removable devices and using non-removable ones, exclude the use of dyes from the composition of removable devices, OT-correctors and install non-removable equipment (braces) without nickel content.

KEYWORDS: *food intolerance, malocclusion, allergy, orthodontic treatment*

ОСОБЕННОСТИ ОРТОДОНТИЧЕСКОГО ЛЕЧЕНИЯ ДЕТЕЙ С ПИЩЕВОЙ НЕПЕРЕНОСИМОСТЬЮ

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РЕЗЮМЕ. Пищевая непереносимость в детском возрасте проявляется различными нарушениями со стороны организма при употреблении продуктов питания. При этом состоянии в организме имеются нарушения работы многих органов и систем, и проблема затрагивает не только работу желудочно-кишечного тракта, но и остальные системы жизнеобеспечения организма. При таких нарушениях меняется метаболизм, обменные процессы. Для стоматологов важно понимать эту проблему, поскольку заболевание изменяет местный *status localis* в полости рта, который является начальным отделом желудочно-кишечного тракта. Это выражается в изменении физико-химических свойств ротовой жидкости, вызывает сухость, чувство жжения со стороны слизистых оболочек полости рта. При ортодонтическом лечении таких пациентов надо внимательно подходить к вопросам изготовления съемных аппаратов и использования несъемных, исключать из состава съемных аппаратов использование красителей, использовать ОТ-корректоры, устанавливать несъемную технику (брекеты) без содержания никеля.

КЛЮЧЕВЫЕ СЛОВА: *пищевая непереносимость, патология прикуса, аллергия, ортодонтическое лечение*

INTRODUCTION

The problem of food intolerance (FI) is widely represented in pediatrics. Its clinical manifestations develop with genetic predisposition. The main target organs are the gastrointestinal tract (GIT), skin, and respiratory system [1]. Adverse reactions to food include immune-mediated food allergy and non-immune-mediated food intolerance. FI is often confused by health care providers, patients, and the public with food allergy, which is one of its manifestations.

The spectrum of FI mechanisms includes:

- food allergies;
- non-allergic reactions to food (caused by chemicals, irritants, toxins);
- enzymopathies and absorption disorders;
- psychogenic reactions to food;
- food intolerance caused by GI diseases.

MEDLINE, EMBASE, and Cochrane databases were used to search for terms related to food allergy and intolerance [3].

Cumulatively, one fifth of the population believe they have adverse reactions to food. Estimates of true IgE-mediated food allergy vary, but in some countries it can be as high as 4–7% among preschool children. The most common food allergens are cow's milk, eggs, peanuts, nuts, soy, shellfish, and fin fish. It has been observed that food allergies are more common in children and can be life-threatening in some cases. However, tolerance to many foods develops with age. Estimates of IgE-mediated food allergies in adults approach 1–2%. Non-IgE-mediated food allergies, such as enterocolitis syndrome caused by food proteins, are less common and are detected predominantly in childhood. Eosinophilic gastrointestinal disorders, including eosinophilic esophagitis, are conditions with mixed IgE- and non-IgE-mediated food allergies that improve when such foods are eliminated from the diet. Food intolerance is nonspecific, and the resulting symptoms resemble other common, medically unexplained complaints, often overlapping with symptoms found in functional disorders such as irritable bowel syndrome. Food intolerance may pose some risk, but because functional disorders are common, more effort is needed to understand the adverse effects of food in functional disorders.

Dentistry has traced the role of FI in the etiology of hypomineralization of molars [4]. Molar incisor hypomineralization (MIH) is an enamel condition characterized by white to brown lesions that indicate rapid caries progression. The permanent first molars and incisors are mostly affected. These enamel defects usually arise from abnormalities in the mineralization or amelogenesis stage. Environmental factors such as respiratory problems, poor diet, infections of any kind and medication intake affecting children aged 3 years and above are also thought to cause the development of MIH.

In the 2021 study, 1,065 saliva samples were obtained from four different cohorts and DNA was extracted from each sample and genotyped for nine different single nucleotide polymorphisms. Association tests and logistic regression implemented in PLINK were used for analysis. Potential interactions were identified between TGFA rs930655 with all markers tested in the cohort. These interactions were not detected in the other cohorts. Associations ($p < 0.05$) were also found between medication intake after age three, suggesting that conditions acquired at an age when children are beginning to socialize may contribute to the development of MIH. The relationship between poor nutrition and infection is also confirmed. The relevance of this concept to the practice of clinical medicine, dentistry, and public health is supported by an impressive body of evidence from both the clinic, laboratory, and field. Improper nutrition can affect any body mechanism that acts as a barrier to the multiplication or progression of infectious agents. This includes the formation of specific antibodies, the number and activity of phagocytes, and the integrity of skin, mucous membranes, and other tissues. Some of the less defined, nonspecific defenses found in body fluids are also affected by poor nutrition. Infectious disease adversely affects nutritional status in several indirect ways. Loss of appetite and food intolerance lead to metabolic changes. Cultural factors lead to substitution of less nutritious diets as a presumed therapeutic measure and to the prescription of laxatives, antibiotics, and other drugs that impair digestion or absorption of certain nutrients. In

well-nourished individuals, body reserves and normal food intake ensure that malnutrition will not lead to GI damage unless the infection is prolonged.

FI has been found to affect 15–20% of the general population and may be due to pharmacological effects of food components, non-celiac gluten sensitivity, or enzyme and transport defects [5]. Significant advances have been made in understanding the scientific basis of gastrointestinal food intolerance due to fermentable short-chain fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs). The most useful diagnostic test for food intolerance is food elimination to achieve improvement in symptoms, followed by gradual resumption of food intake. A low-FODMAP diet is effective, but it affects the GI microbiota and restoring FODMAP tolerance is part of the treatment strategy.

There is growing evidence for the use of a low-FODMAP diet to treat functional gastrointestinal symptoms in suspected food intolerance. Exclusion diets should be used for as short a time as possible to induce improvement in symptoms and should be followed by gradual reintroduction of foods to establish individual tolerance. This will increase dietary diversity, ensure adequate nutrition and minimize the impact on the GI microbiota.

With regard to the orthodontic treatment of children with FI, it should be noted that the orthodontist most often encounters food allergies, followed by non-food agents: dust, pollen, animal hair, certain types of drugs.

AIM

To describe the specifics of orthodontic treatment for children with food allergies.

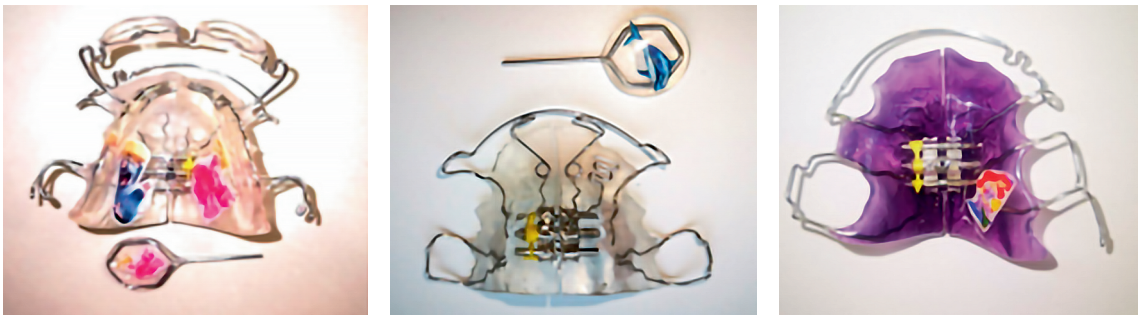
MATERIALS AND METHODS

The clinic analyzed 132 health questionnaires filled out by legal representatives (parents) of children from 8 to 14 years of age. A group of 8–11 years old patients was identified, a total of 54 patients who were treated with removable appliances. It should be noted that 27 patients 8–11 years old, which amounted to 50% of cases, had allergic reactions to food and non-food agents and medications in the questionnaires. Of this group, 18 had confirmation of allergy as an independent disease, and the children were registered and treated by an allergologist.

RESULTS

In the group of patients with confirmed allergic manifestations who required treatment with removable appliances, orthodontic appliances were fabricated without the use of dyes (Fig. 1).

In addition to the fact that appliances should be fabricated without the use of chemical staining reagents, the technique of changing the position of the arch adjacent to the incisors and the claspers that are adjacent to the molars should be considered during treatment. These are the teeth that, according



a/а *b/б* *c/в*

Fig. 1. Orthodontic removable devices: *a*, *b* — without dye content (recomendetion for patients with food intolerance); *c* — a device with the use of a dye

Рис. 1. Ортодонтические съемные аппараты: *а, б* — без содержания красителей (рекомендованы для пациентов с пищевой непереносимостью); *в* — аппарат с применением красителя

to the literature, have a MIH state. In such a case, when the appliance elements contact at the same points, we may get even more enamel damage in these teeth during orthodontic treatment (Fig. 2). It should be noted that clinically the MIH condition is not always pronounced, so such recommendations should be considered in the treatment process for all patients.

In the same group of patients, myofunctional corrector appliances were used as indicated (Fig. 3). These are hypoallergenic single-patient devices made of FDA-approved medical-grade materials (FDA (*Food and Drug Administration*) Code of Federal Regulations, Title 21), free of bisphenol (BPB, BPF, or BPS), phthalates, latex, and silicone, and free of hazardous chemicals identified by the FDA [6]. The OT-corrector series devices have passed many different biocompatibility tests (cytotoxicity, pyrogenicity, Kligman test, injection, and chemical characterization extraction and leaching test) and in the opinion of a GLP accredited laboratory. All were found to be in compliance with ISO 10993-1:2018 (as surface devices with prolonged

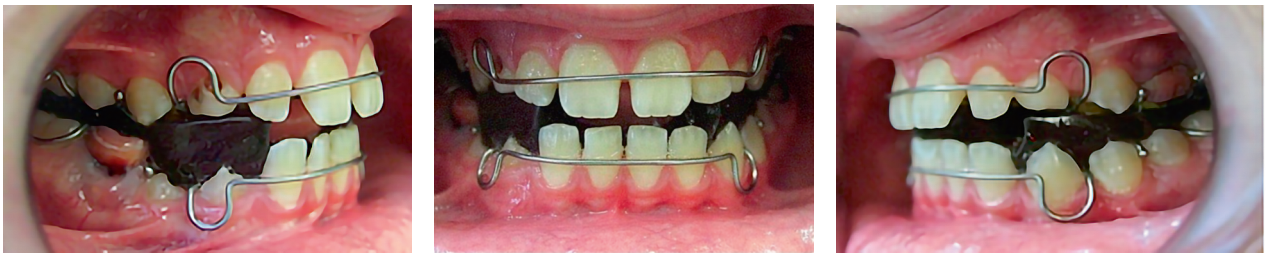


Fig. 2. Individual removable orthodontic device. Rigid metal elements adhere to the enamel of the teeth

Рис. 2. Индивидуальный съемный ортодонтический аппарат. Металлические жесткие элементы прилегают к эмали зубов

a/а *b/б* *c/в*

Fig. 3. Various types of OT- correctors: corrector of bad habits (*a*), Nite-Guide corrector (*b*), Occlus-O-Guide corrector (*c*), which are recomendetion for patients with food intolerance

Рис. 3. Различные виды ОТ-корректоров: корректор вредных привычек (*а*), Nite-Guide корректор (*б*), Occlus-O-Guide корректор (*в*), которые рекомендованы для пациентов с пищевой непереносимостью

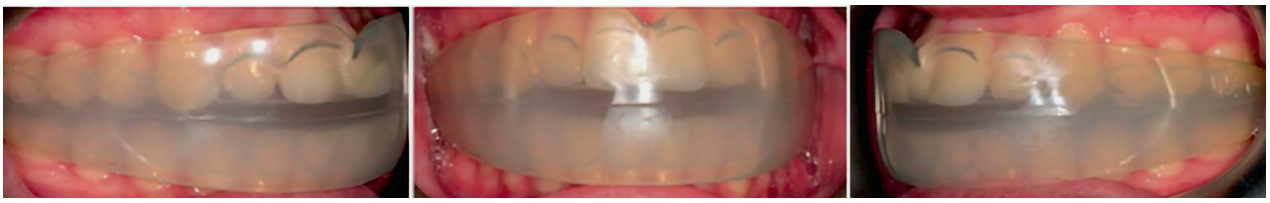


Fig. 4. Myofunctional OT-corrector. The device does not have a point fit to the teeth. It is preferred for patients with food intolerance

Рис. 4. Миофункциональный ОТ-корректор. Аппарат не имеет точечного прилегания к зубам. Предпочтителен для пациентов с пищевой непереносимостью

mucosal contact). Biological considerations for this standard include studies for cytotoxicity, sensitization, irritation, acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, implantation, and chronic toxicity and are considered biocompatible.

These devices are designed to interact gently with the enamel of the teeth, without specific points of support (Fig. 4). In addition, the design of the appliance itself allows for home remodeling procedures. Therefore, in FI patients, the use of such appliances made

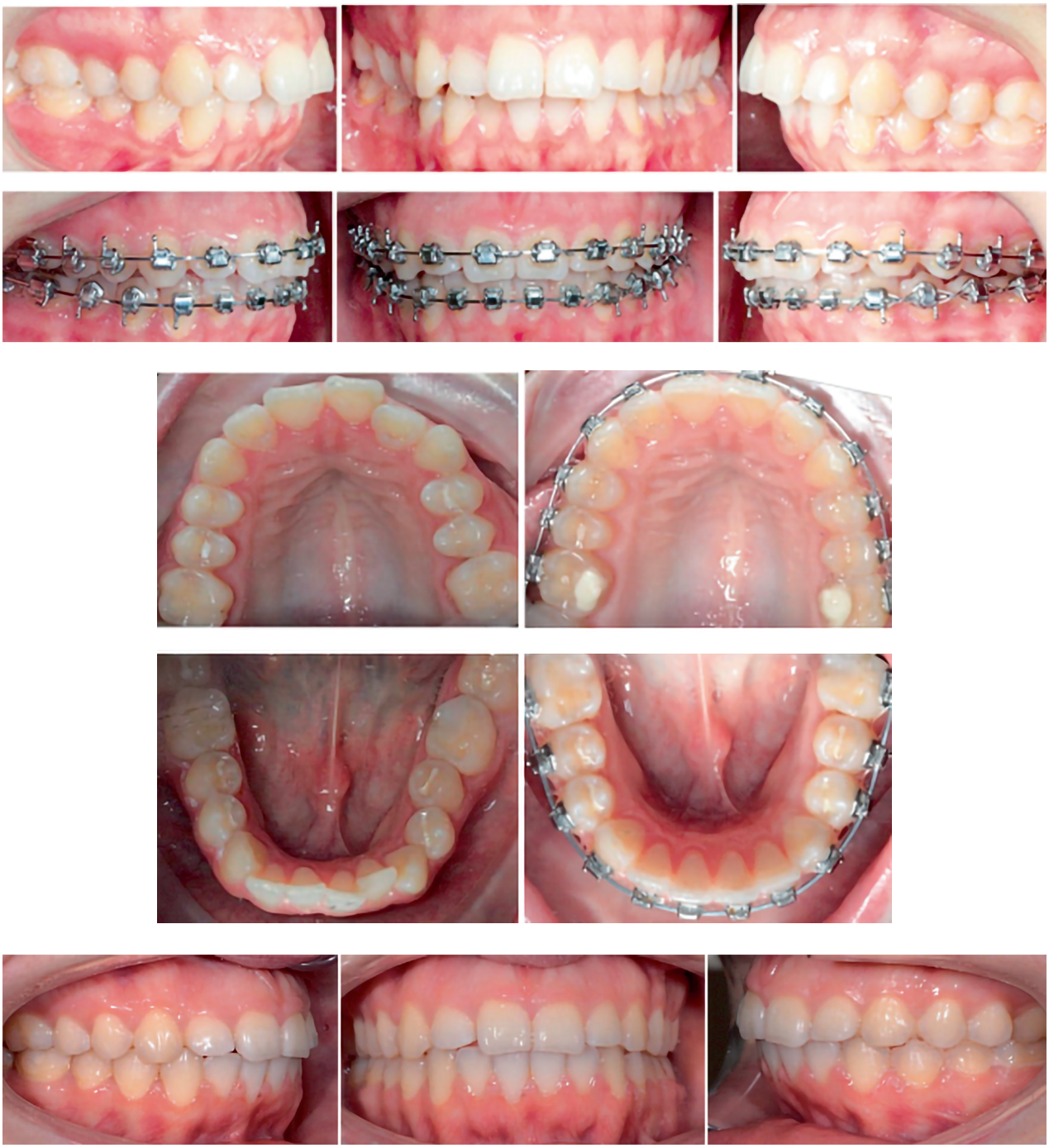


Fig. 5. The result of orthodontic treatment using nickel-free braces in patients with food intolerance

Рис. 5. Результат ортодонтического лечения с применением брекетов, не содержащих никель, у пациентов с пищевой непереносимостью

of soft material is preferable if they are suitable for the treatment of occlusal disorders and do not cause any enamel deterioration during treatment if a MIH condition is diagnosed.

In a group of 78 patients aged 11–14 years, fixed appliances were placed as indicated. In this group, 23 children had an established allergy-related diagnosis. A nickel-free bracket system was used (Fig. 5).

Braces are chosen in a design where their site, which is attached to the tooth enamel, has a distinct pattern for secure retention. This helps patients with MIH to avoid debonding of the bracket throughout the treatment phase (Fig. 6).

We would like to emphasize the special protocol of arc replacement. As you know, the first arc that is placed on patients at the initial stage is an arc containing nickel. This element is the first to be allergic to it. Instead of nickel-containing arches, braided flexi steel arches should be used, which before the era of nickel-containing arches were used in the initial stages of orthodontic treatment. Thereafter, treatment should continue on full-length steel arches. This applies to all patients with severe FI. In special cases, an allergic reaction to the metals in the steel arches may occur. In this case, treatment with customized eliners (Fig. 7) is possible. During treatment, they can be used as a device for home reMODELING IN PATIENTS WITH MIH.

After braces are removed, fixed and removable retainers are fitted according to clinical guidelines (Fig. 8). The non-removable retainer is made of braided steel wire. For patients with MIH, this type of retention should be used with caution because the fixed retainer is fixed to the incisors on the palatal side, making it difficult to perform hygiene procedures.

In addition, the prolonged presence of steel in the oral cavity contributes to the release of metal ions into the oral fluid [2], which is unacceptable for patients with FI. In such cases, the fixed retainer should be replaced with a retention mouth guard.

CONCLUSION

Patients diagnosed with food intolerance have a variety of clinical manifestations that are not specific to the disease. Orthodontists treating these patients should pay careful attention to the information in the patient's health questionnaire and, when removable appliances are indicated, opt for OT-correctors or customized removable appliances without the use of dyes. At older ages, when fixed appliances or eliners are indicated, in the absence of MIH, nickel-free braces can be

Fig. 6. Pronounced bracket pad recommended for patients with MIH

Рис. 6. Выраженная площадка брекета, рекомендованная для пациентов с МІН

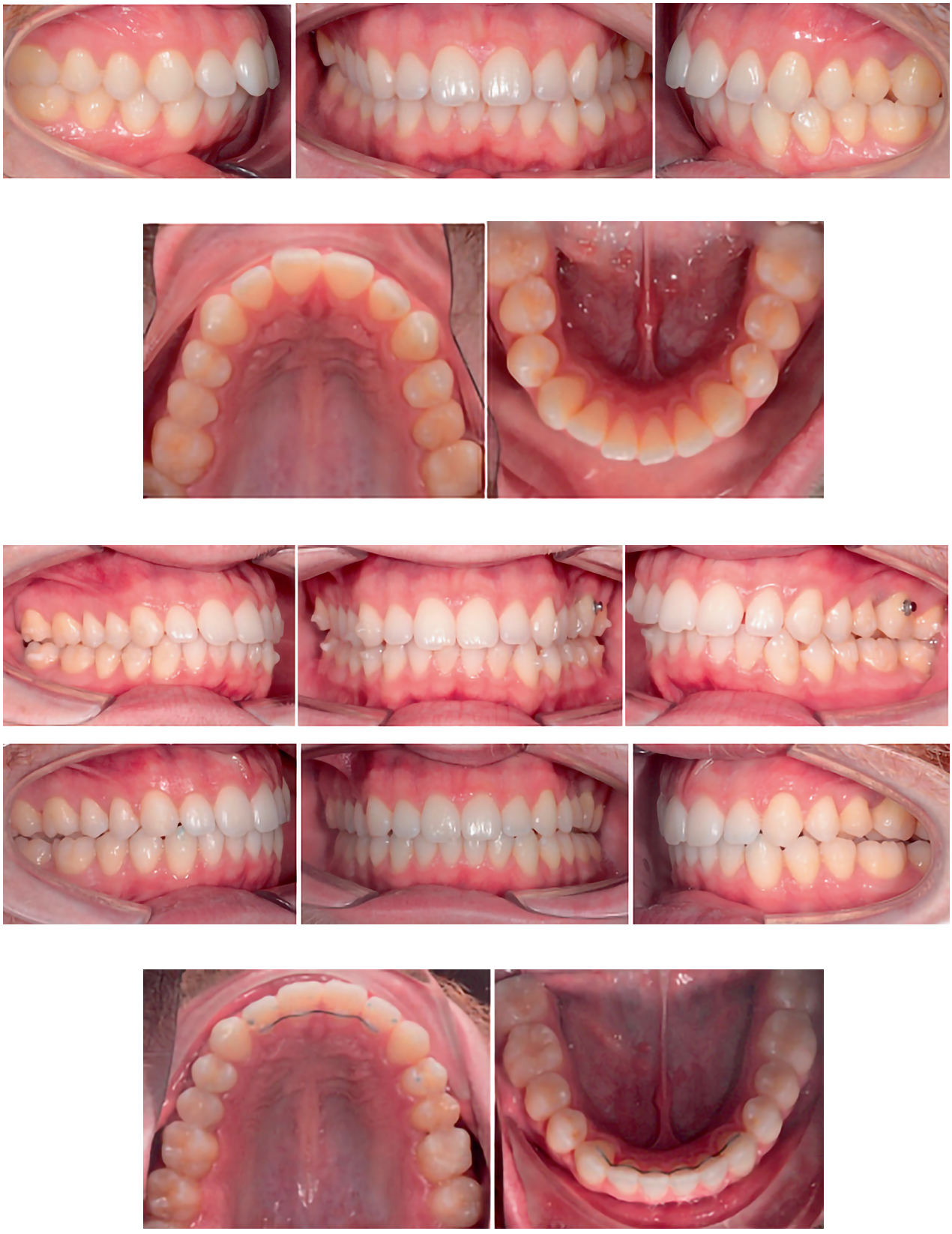
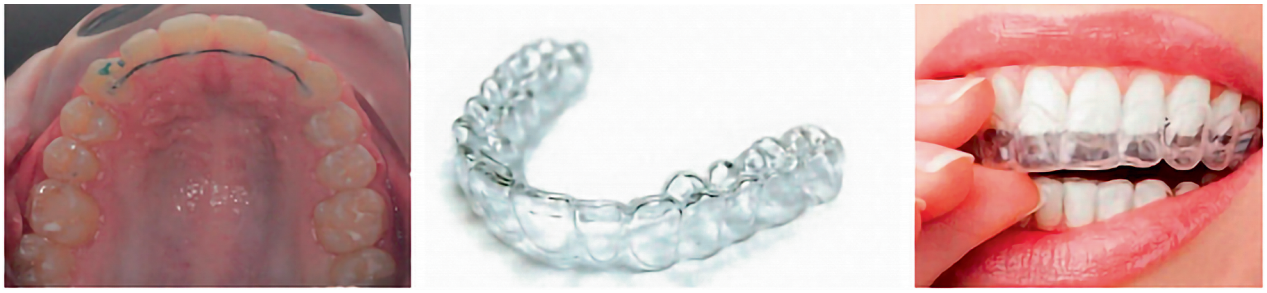


Fig. 7. The stages of treatment of a patient with MIH on aligners

Рис. 7. Этапы лечения пациента с МІН на элайнерах



а/a *б/b*

Fig. 8. Non-removable retainer (*a*); removable retainer in the form of a mouth guard (*b*)

Рис. 8. Несъемный ретейнер (*а*); съемный ретейнер в виде капы (*б*)

fixed and steel bars can be used; in other cases, eliners can be used. In the retention period in these patients, removable retainers in the form of mouthguards are preferable.

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

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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.

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FEATURES OF MILD AND MODERATE COURSE OF COVID-19 IN CHILDREN OF DIFFERENT AGES

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ABSTRACT. ***Introduction.*** Despite the fact that the pandemic of the new coronavirus infection has ended, this problem has not lost its relevance. In Russia, 24,645,303 people have been infected with the new coronavirus infection during the entire course. As of November 2024, this virus has been identified in 35,689 people in the Russian Federation. COVID-19 is currently subject to general infectious laws such as epidemiology and seasonality, and the ability of this virus to transmit and quickly mutate also contributes to the prevalence of this infection. ***Objective.*** To describe the clinical features of mild and moderate course of COVID-19 in children of different ages. ***Materials and methods.*** Complaints and clinical picture of the disease were studied in 270 children of different age groups with a new coronavirus infection confirmed by PCR. ***Results.*** Analysis of patient complaints at the onset of the disease showed that children with Covid-19 most often complained of an increase in body temperature (75.2%). Respiratory complaints were noted with high frequency: runny nose (62.2%), cough (48.1%), less common were sore throat (17.4%) and loss of smell (anosmia) (11.5%), chest pain (5.2%), loss of taste (ageusia) (3.7%). The incidence of shortness of breath was 1.9%. ***Conclusions.*** The leading complaints in children with confirmed new coronavirus infection at the onset of the disease were respiratory complaints, which do not allow distinguishing this disease from a banal acute respiratory viral infection of mild to moderate severity, with symptoms relieving by the 14th day of the disease. The incidence of pneumonia among patients is 28.14%, the most significant number of pneumonias was detected in adolescents (p=0.013); they also have the most frequent cough.

KEYWORDS: *COVID-19, clinical course, mild and moderate course, pneumonia, age characteristics*

ОСОБЕННОСТИ ЛЕГКОГО И СРЕДНЕТЯЖЕЛОГО ТЕЧЕНИЯ COVID-19 У ДЕТЕЙ РАЗНОГО ВОЗРАСТА

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РЕЗЮМЕ. ***Введение***. Несмотря на то что пандемия новой коронавирусной инфекции окончилась, эта проблема не утратила своей актуальности. В России за все время новой коронавирусной инфекцией заразились 24 645 303 человека. По состоянию на ноябрь 2024 года в Российской Федерации данный вирус идентифицировали у 35 689 человек. COVID-19 в настоящее время подвергается общим инфекционным законам, таким как эпидемиология и сезонность. Вклад в распространенность этой инфекции вносит способность вируса SARS-CoV-2 к трансмиссии и быстрой мутации. ***Цель*** — описать клинические особенности легкого и среднетяжелого течения COVID-19 у детей разного возраста. ***Материалы и методы***. Жалобы и клиническая картина заболевания изучены у 270 детей разных возрастных групп с подтвержденной методом полимеразной цепной реакции (ПЦР) новой коронавирусной инфекцией. ***Результаты.*** Анализ жалоб пациентов в дебюте заболевания показал, что наиболее часто дети, больные COVID-19, жаловались на повышение температуры тела (75,2%). С высокой частотой отмечались респираторные жалобы: насморк (62,2%), кашель (48,1%), реже встречались боль в горле (17,4%,) и потеря обоняния (аносмия) (11,5%), боль в грудной клетке (5,2%), потеря вкуса (агевзия) (3,7%). Частота одышки составила 1,9%. ***Выводы.*** Ведущими у детей с подтвержденной новой коронавирусной инфекцией в дебюте заболевания были респираторные жалобы, не позволяющие отличить это заболевание от банальной острой респираторной вирусной инфекции легкой и среднетяжелой степени тяжести, с купированием симптомов к 14-му дню заболевания. Частота пневмонии среди пациентов составляла 28,14%, наиболее значимое количество пневмоний выявлено у подростков (p=0,013), у них же кашель отмечается наиболее часто.

КЛЮЧЕВЫЕ СЛОВА: COVID-19*, клиническое течение, легкая и среднетяжелое течение, пневмония, возрастные особенности*

INTRODUCTION

Analysis of the COVID-19 pandemic statistics showed that children and adolescents showed significantly lower susceptibility to SARS-CoV-2, accounting for less than 10% of the total number of diagnosed cases. This significant difference from the incidence pattern in adults is attributed to a complex set of factors that are still under active investigation. The milder course of the disease in children is primarily due to the immunologic abilities of the pediatric organism.

Children rarely have chronic diseases that have a pathogenetic effect on the body and contribute to the activation of immunologic processes and are not exposed to long-term harmful factors such as tobacco smoking, polluted air and chronic respiratory diseases. This ensures more efficient lung function and reduces the risk of severe complications such as pneumonia and acute respiratory distress syndrome (ARDS), which are often seen in adult patients. The more developed regenerative capacity of lung tissue in children also plays an important role in rapid recovery from infection [1, 2]. Coronavirus infection, especially in winter, is observed quite frequently, and this phenomenon is associated with several factors concerning both children and the elderly. Studies show that children have higher levels of antibodies to coronaviruses than adults. This may be due to the fact that children's immune system responds more actively to viral infections, which allows for a wider range of protective antibodies to form. Interestingly, antibodies produced in response to seasonal coronaviruses may also offer some protection against COVID-19. This cross-effect of antibodies may explain why children tend to tolerate COVID-19 more easily than the elderly individuals [2, 3]. Among other things, older people have a weakened immune response, which can lead to a higher risk of developing severe forms of the disease. They have lower levels of partially cross-reactive antibodies, which may contribute to antibody-dependent immune enhancement. This condition occurs when antibodies, binding to the virus, do not neutralize it but, on the contrary, promote its penetration into cells and intensify the infection [4]. Children are most often infected with coronaviruses from adult family members, that is, the second or third generation of the virus. It is important to note that such viruses, as a rule, have a lower pathogenicity, which also reduces the risk of a severe course of the disease in children. However, it should be remembered that children and adolescents have their own peculiarities concerning the expression of the angiotensin-converting enzyme 2 (ACE2) gene, which is the main receptor for SARS-CoV-2 [5, 6]. Studies show that ACE2 expression in nasal epithelium increases with age. Children in the younger age group (under 10 years old) have the lowest ACE2 levels, whereas adolescents (10 to 17 years old) have higher but still much lower levels than adults. This may explain why children are less susceptible to severe forms of COVID-19. However, in the lower respiratory tract, decreased ACE2 expression may be associated with an increased risk of severe acute respiratory distress syndrome and lung injury [6]. In addition, there are age-related features of innate immunity in children. For example, they have a higher constitutional activity of lymphocytes, especially natural killer cells (NK cells), compared to adults. This may explain why children's bodies are more effective in fighting viral infections. Nevertheless, lymphopenia is sometimes recorded in newborn children, which may indicate certain peculiarities of immune response formation at this age. How children respond to vaccination is also an important aspect. COVID-19 vaccines tend to elicit a strong immune response in them, which may be related to their active immune system. This, in turn, may serve as an additional defense against different strains of coronavirus. Studies show that even after an illness, children can retain protective antibodies for a long time, which also reduces the risk of re-infection [7, 8].

Thus, the interaction between coronaviruses and the immune systems of children and the elderly is a complex and multifaceted process. On the one hand, children have several advantages in the form of a more active immune response and lower ACE2 expression, which reduces the risk of severe disease. On the other hand, older adults face a weakened immune system and a higher risk of complications. These differences emphasize the importance of an

individualized approach to COVID-19 prevention and treatment according to age group [9]. Furthermore, understanding these mechanisms may help in developing more effective vaccination and treatment strategies, as well as raising awareness on ways to better protect vulnerable populations, including the elderly and children. It is important to continue investigating the impact of coronaviruses on different age groups to improve our knowledge of immune response mechanisms and to develop more effective virus control methods in the future.

In 2021, the world faced new challenges in the fight against COVID-19, especially after the emergence of new strains of the virus, such as Delta and Omicron. The Delta strain was highly contagious and contributed to faster onset of symptoms. This led to an increase in the number of cases of moderate to severe forms of the disease. The statistics for children were particularly alarming, with the proportion of cases among them rising to 11%. However, by the end of 2021, when the Omicron strain came to the fore, this figure had increased to almost 25%, indicating the significant impact of the new variants of the virus on the pediatric population. The Omicron strain showed a slightly different behavior compared to previous versions of the virus. It preferentially multiplies in the upper respiratory tract, resulting in a milder course of disease. This means that patients, including children, are less likely to have severe lower respiratory tract lesions, which in turn reduces hospitalizations and serious complications. This is especially true for unvaccinated children and those without pre-existing adaptive immunity [10–13]. The clinical course of COVID-19 in children is largely similar to that of common respiratory infections [1]. The most common clinical manifestations include fever, generalized weakness, fatigue, headache, sore throat, runny and stuffy nose, myalgia, and cough, which may be dry or with a small amount of sputum. In some cases, children may also show signs of conjunctivitis. Interestingly, among the first symptoms of COVID-19 may include rarer manifestations such as confusion, headaches, hemoptysis, palpitations, diarrhea, loss of appetite, vomiting, and abdominal pain. According to studies, 69% of patients with COVID-19 had gastrointestinal symptoms combined with an elevated body temperature above 38.5 °C. Skin manifestations may also be observed in 13% of patients, emphasizing the diversity of the clinical picture [13–17]. One of the pathognomonic symptoms of COVID-19 in adults is hyposmia or anosmia (decreased or absent sense of smell) and dysgeusia or agueusia (altered or absent taste). These symptoms can also occur in children, although they may not always realize and report their sensations due to their age. However, among children with COVID-19, changes in smell or taste, nausea, vomiting, and headache were more common than other symptoms. In most cases of mild to moderate forms of the disease, recovery occurs within 1–2 weeks. However, it is worth noting that some patients may experience long-term symptoms known as post-covid syndrome, which can manifest as fatigue, shortness of breath, concentration problems, and other symptoms that may persist for months after initial recovery.

Thus, observations of the course of COVID-19 in children indicate that it is important to continue to monitor their spread and impact on different populations, especially on children, although new strains such as Omicron may cause less severe forms of disease. Vaccination and precautionary measures remain key to controlling the pandemic and reducing the incidence of disease.

Involvement of the GI tract in the pathologic process in COVID-19 has been attributed by most researchers to the detection of the virus in the intestine [18–20]. In 22–54.5% of cases, SARS-CoV-2 virus can be detected in the stool of patients with COVID-19, and sometimes the virus is detected in the stool even after the results of respiratory swabs become negative [19]. In patients with gastrointestinal symptoms, the overall time between symptom onset and virus clearance is significantly longer than in patients with respiratory manifestations alone [21, 23]. The relationship between gastrointestinal symptoms during SARS-CoV-2 virus infection and the production of proinflammatory cytokines [24, 25], the development of intestinal epithelial inflammation [26], and impaired intestinal wall permeability [22, 27, 28] has been actively discussed in the literature. Most of these studies were performed in adult patients with severe disease, and there are a few studies in the pediatric population.

AIM

To describe the clinical features of mild and moderate course of COVID-19 in children of different ages.

MATERIALS AND METHODS

Complaints and clinical picture of the disease were studied in 270 children of different age groups with new coronavirus infection confirmed by polymerase chain reaction (PCR). Children were randomized into 4 groups: group 1 (1–4 years old children), group 2 (5–9 years old children), group 3 (10–14 years old children), and group 4 (15–17 years old children). Identification of SARS-CoV-2 virus from the pharynx and nose by PCR occurred in all children in the first 1–3 days from the onset of clinical symptoms.

The study was approved by the local ethical committee of Federal State Budgetary Educational Institution of Higher Education St. Petersburg State Pediatric Medical University of the Ministry of Healthcare of the Russian Federation. Children were examined in dynamics: from the onset of the disease to recovery from COVID-19 infection. Patient data were collected: complaints, anamnesis, clinical status, laboratory diagnostics.

Statistical processing of data was carried out using IBM SPSS Statictics 26 application program package. Student's t-criterion was used to compare the average indices of quantitative signs in the studied groups with the assessment of the reliability of differences ($p < 0.05$).

RESULTS

Analysis of patient complaints at disease onset showed that children with COVID-19 most often complained of an increase in body temperature (75.2%). Respiratory complaints were noted with high frequency: runny nose (62.2%), cough (48.1%), sore throat (17.4%,) and loss of sense of smell (anosmia) (11.5%), chest pain (5.2%), loss of taste (agenesis) (3.7%) were less frequent. The frequency of dyspnea was 1.9%. Analysis of temperature response in children of different age groups showed no significant age differences. Temperature over 40 °C was noted with a frequency of 0–5.6%; 39.0–39.9 °C was noted with a frequency of 9.7–27.9%; 38.0–38.9 °C was noted in 36.1–37.7% of cases; and 37.0–37.9 °C was noted in 9.8-25% of cases. Normal body temperature was noted in 21.3–29.5% of patients. At the same time, the nature of respiratory complaints in different age groups of children differed significantly (Table 1).

As follows from the table, cough was significantly more frequent in the group of children aged over 15 years (60.7%, $p=0.043$), and less frequent in children aged 10–14 years. The results are consistent with literature data on the milder course of COVID-19 in young children than in adolescents and adults. The frequency of runny nose was similar in all studied groups and ranged from 54.2 to 75.4%. Chest pain ($p=0.007$) and sore throat ($p < 0.001$) were significantly more frequent in group 4 adolescents. Younger children were worse at

Table 1. Characteristics of respiratory complaints in children with new coronavirus infection in different age groups

Таблица 1. Характеристика респираторных жалоб у детей с новой коронавирусной инфекцией в разных возрастных группах

Возрастная группа / Age group	Кашель / Cough (n/%)	Насморк / Runny nose (n/%)	Аносмия / Anosmia (n/%)	Агевзия / Ageusia (n/%)	Боль в грудной клетке/ Chest pain (n/%)	Одышка / Ortness of breath (n/%)	Боль в горле / Sore throat (n/%)
Группа 1 (1–4 года) / Group 1 (1-4 years)	28/45,9%	35/57,4%	0/0%	0/0%	0/0%	0/0%	3/4,9%
Группа 2 (5–9 лет) / Group 2 (5–9 years)	37/51,4%	39/54,2%	6/8,3%	3/4,2%	4/5,6%	0/0%	8/11,1%
Группа 3 (10–14 лет) / Group 3 (10–14 years)	28/36,8%	48/63,2%	15/19,7%	3/3,9%	2/2,6%	2/2,6%	18/11,1%
Группа 4 (15–17 лет) / Group 4 (15–17 years)	37/60,7%	46/75,4%	10/16,4%	4/6,6%	8/13,1%	3/4,9%	18/29,5%
p	p=0,043	p=0,068	p=0,002	p=0,284	p=0,007	p=0,116	p <0,001

identifying and localizing pain syndrome. Group 3 and 4 children were significantly more likely to have anosmia than group 1 and 2 children (p=0.002). No differences in the frequency of other respiratory complaints were found.

Gastroenterological complaints at disease onset in the examined children occurred with a frequency of 3.7–13.3%, with abdominal pain predominating (13.3%), liquid stools with a frequency of 11.1% and vomiting with a frequency of 10.7%. Adolescents carrying a new coronavirus infection were significantly more likely to have nausea – 13.1% of cases (p=0.043), young children (group 1) identified nausea worse: the frequency of nausea was significantly lower – 1.6%. Children in group 3 (17.1%) and group 4 (14.8%) had significantly more frequent complaints of headaches (p=0.001) than children in groups 1 and 2 (1.4–3.3%). Rare complaints included myalgia/joint pain (2.6%), dizziness (1.9%). There were no significant differences in the frequency of these complaints between age groups.

Of the 270 children examined, 218 (81%) developed clinical manifestations of the infectious process on the 3rd-5th day from the moment of contact with patients with a new coronavirus infection. 38 children (14%) had respiratory and intoxication complaints on the 1st–2nd day. Only 14 children (5%) developed complaints on the 6th–7th day after contact with the source of infection. Family members were the source of infection in 125 children (46%), while 145 children (53%) had contacts in children's institutions and non-family sources of infection.

The life history (anamnesis vitae) of children carrying a new coronavirus infection revealed a large number of unfavorable factors: pathological course of pregnancy was noted in 38.5%; previous artificial feeding was noted in 27.0%; worm and parasitic infestations were noted in 17.6%; anemia in the first year of life was noted in 14.8% of children; frequent acute respiratory viral infections at an early age were noted in 11.9% of children.

Unfavorable factors of anamnesis were equally frequent in all age groups.

As a result of objective examination, we found that at the debut of the disease, most children (56%) in different age groups were in satisfactory condition and tolerated the new coronavirus infection in a mild form. In 115 children (44%) the severity of the disease was considered as average. The severity of the disease had no significant differences in all age groups (Table 2).

During physical development assessment, 261 (96.6%) of 270 children had an average level of physical development. In 9 (3.33%) children, the level of physical development was above average, and 7 (2.59%) children were obese (BMI more than +2.1SDS). There were no children with a level of physical development below average in the study.

Table 2. Severity of the disease in children of different age groups

Таблица 2. Степень тяжести заболевания у детей разных возрастных групп

Возрастная группа / Age group	Степень тяжести / Severity (n)	Среднее значение возрастной группы / Average age group	95% доверительный интервал / 95% confidence interval	p
Группа 1 (1–4 года) / Group 1 (1–4 years)	Легкая / light (26)	2,23	1,83–2,63	p=0,209
	Средней тяжести / Moderate (35)	1,92	1,58–2,25	
Группа 2 (5–9 лет) / Group 2 (5–9 years)	Легкая / Light (48)	7,15	6,72–7,57	p=0,816
	средней тяжести / Moderate (24)	7,25	6,66–7,84	
Группа 3 (10–14 лет) / Group 3 (10–14 years)	Легкая / Light (50)	11,84	11,43–12,25	p=0,090
	Средней тяжести / Moderate (26)	12,46	11,85–13,07	
Группа 4 (15–17 лет)/ Group 4 (15–17 years)	Легкая / Light (31)	16,03	15,77–16,29	p=0,096
	Средней тяжести / Moderate (30)	16,33	16,07–16,60	

Note: The confidence interval of the mean assumes that the sample means follow a t-distribution with N–1 degrees of freedom.
Примечание: доверительный интервал среднего предполагает, что выборочные средние следуют t-распределению с N–1 степенями свободы.

The skin of all examined children was of normal color, without rash. Changes on the nasopharyngeal mucosa were equally frequent in the age groups: pharyngeal hyperemia was found from 52 to 71%, tonsil hypertrophy was found from 67.1 to 82%, and tonsil plaques were found in 4.2–6.6% (p >0.05). Respiratory rate and the ratio of heart rate (HR) to respiratory rate (RR) corresponded to normal in all patients, tachycardia and tachypnea in the examined corresponded to the degree of fever. Saturation was normal in all children (SaO_2 97–98%).

The results of objective examination of the respiratory system (RS) and cardiovascular system (CVS) at disease debut are presented in Figure 1 (p <0.005).

Vesicular breathing was noted significantly (p <0.005) in patients in groups 2 and 3. Harsh breathing was noted in children in group 4, which is consistent with the radiologic diagnosis of pneumonia.

Loss of resonanse in groups 1 and 4 was significantly noted (p=0.046).

The results of objective examination of gastrointestinal (GI) organs in patients at COVID-19 debut are

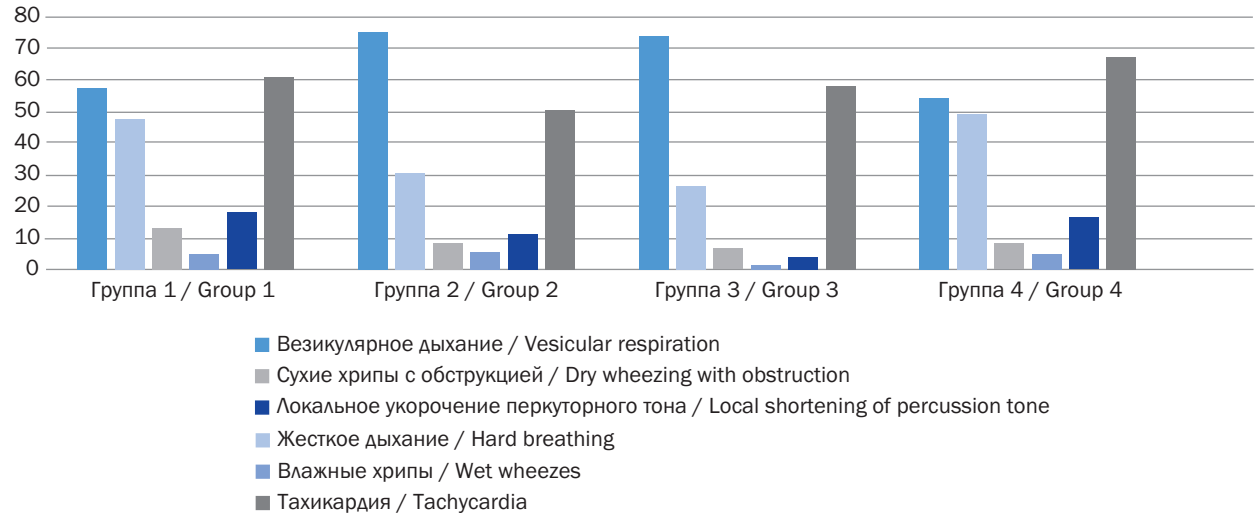

Fig. 1. Results of an objective study of respiratory system and cardiovascular system at the onset of COVID-19 disease

Рис. 1. Результаты объективного исследования дыхательной системы и сердечно-сосудистой системы в дебюте заболевания COVID-19

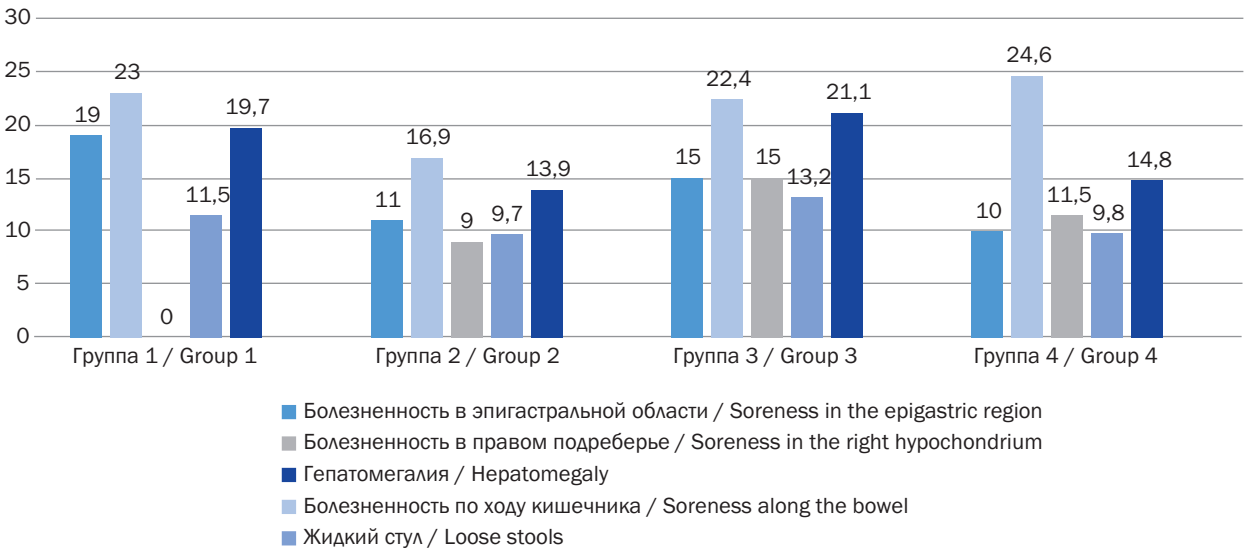

Fig. 2. Objective assessment of the gastrointestinal tract in patients at the onset of COVID-19

Рис. 2. Объективная оценка органов желудочно-кишечного тракта у больных в дебюте COVID-19

presented in Figure 2. We analyzed such symptoms as abdominal bloating, palpatory pain in the epigastric region, along the course of the intestine, in the right subcostal area and stool character (p >0.005).

The stool characteristic according to the Bristol scale had no significant differences in the age groups of patients. Nevertheless, it should be noted that liquid stools (6–7 on the Bristol scale) were observed with a frequency from 0.7 to 21.1% in different groups.

Clinical blood counts in the debut of the disease in patients carrying a new coronavirus infection revealed leukocytosis in 7% of cases, leukopenia in 17% of cases, lymphopenia in 3.2% of cases, lymphocytosis in 5.2% of cases, neutropenia in 4.3% of cases, neutrophilosis in 9% of cases, increased erythrocyte sedimentation rate (ESR) in 25% of cases, and anemic syndrome in 11% of cases.

Thus, on the basis of complaints, anamnesis, objective and routine laboratory examination we were able to identify typical syndromes characteristic of acute respiratory diseases: intoxication syndrome, upper respiratory tract lesion syndrome (catarrhal syndrome), GI lesion syndrome, focal lung tissue thickening syndrome (28.14%) and inflammatory changes in the blood. The presence of intoxication, focal pulmonary tissue lesion

Table 3. Characteristics of stool according to the Bristol stool scale in children at the onset of COVID-19

Таблица 3. Характеристика стула по Бристольской шкале у детей в дебюте COVID-19

Показатели / Indicators	**Возрастная группа / Age group**	**Значение стула по Бристольской шкале / Bristol Stool Scale Value**							**Всего (n) / Total (p)**
		1	**2**	**3**	**4**	**5**	**6**	**7**	
Число наблюдаемых / Number observed (n/%)	Группа 1 (1–4 года) / Group 1 (1–4 years)	0/0	2/3,3	14/23,0	30/49,2	3/4,9	1,1,6	11/18	61
	Группа 2 (5–9 лет) / Group 2 (5–9 years)	1/1,4	9/12,7	21/29,6	23/32,4	2,8	0/0	15/21,1	71
	Группа 3 (10–14 лет) / Group 3 (10–14 years)	2/2,6	7/9,2	16/21,1	28/36,8	7/9,2	1/1,3	15/19,7	76
	Группа 4 (15–17 лет) / Group 4 (15–17 years)	3/1,1	20/7,4	69/25,7	109/40,5	16/5,9	2/0,7	50/18,6	269

Примечание / Note: p=0,407.

Table 4. Results of X-ray diagnostics of pneumonia in children with COVID-19

Таблица 4. Результаты рентгенологической диагностики пневмоний у детей с COVID-19

Возрастная группа / Age group	**Всего / Total (n/%)**	**Правосторонняя / Right-sided (n/%)**	**Левосторонняя / Left-hand (n/%)**	**Двусторонняя / Two-sided (n/%)**
Группа 1 (1–4 года) / Group 1 (1–4 years)	21/34,4%	4/6,6%	5/8,2%	12/19,7%
Группа 2 (5–9 лет) / Group 2 (5–9 years)	15/20,8%	2/2,8%	2/2,8%	11/15,3%
Группа 3 (10–14 лет) / Group 3 (10–14 years)	15/19,7%	3/3,9%	4/5,3%	8/10,5%
Группа 4 (15–17 лет) / Group 4 (15–17 years)	25/41%	5/8,2%	3/ 4,9%	15/24,6%
	p=0,013	p=0,485	p=0,576	p=0,158

syndrome, and inflammatory reaction in blood analysis were indications for radiographic examination of the chest organs. Out of 270 patients, 76 (28.1%) children were diagnosed with acute out-of-hospital pneumonia.

Pneumonia was most often radiologically detected in age group 4, which is consistent with the presence of more cough complaints in adolescents in the same group. Bilateral pneumonia was detected most frequently in each age group (p <0.05). The results of radiologic diagnosis of pneumonia are presented in Table 4.

The frequency of S1–S7, S9, S10 lesions was similar in all age groups, but the S8 segment was significantly more frequently affected in children of group 4 (8.2%; p=0.050). Morphological characteristics of pneumonias in children with COVID-19 in different age groups had no differences, but complications in the form of pleurisy were noted only in group 4 (1.6%) (Table 5).

The dynamics of the disease is presented in Figure 3.

Table 5. Morphological characteristics of pneumonia in children with COVID-19 in different age groups

Таблица 5. Морфологическая характеристика пневмоний у детей с COVID-19 в разных возрастных группах

Возрастная группа/ Age group	**Полисегментарная / Polysegmental**	**Нижнедолевая / Lower lobe**	**Среднедолевая / Mid-shaft**	**Плеврит / Pleurisy**
Группа 1 (1–4 года) / Group 1 (1–4 years)	12/19,7%	4/6,6%	1/1,6%	0/0,0%
Группа 2 (5–9 лет) / Group 2 (5–9 years)	9/12,5%	2/2,8%	0/0,0%	0/0,0%
Группа 3 (10–14 лет) / Group 3 (10–14 years)	6/7,9%	4/5,3%	1/1,3%	0/0,0%
Группа 4 (15–17 лет) / Group 4 (15–17 years)	14/23,0%	6/5,3%	0/0,0%	1/1,6%
	p=0,062	p=0,383	p=0,572	p=0,329

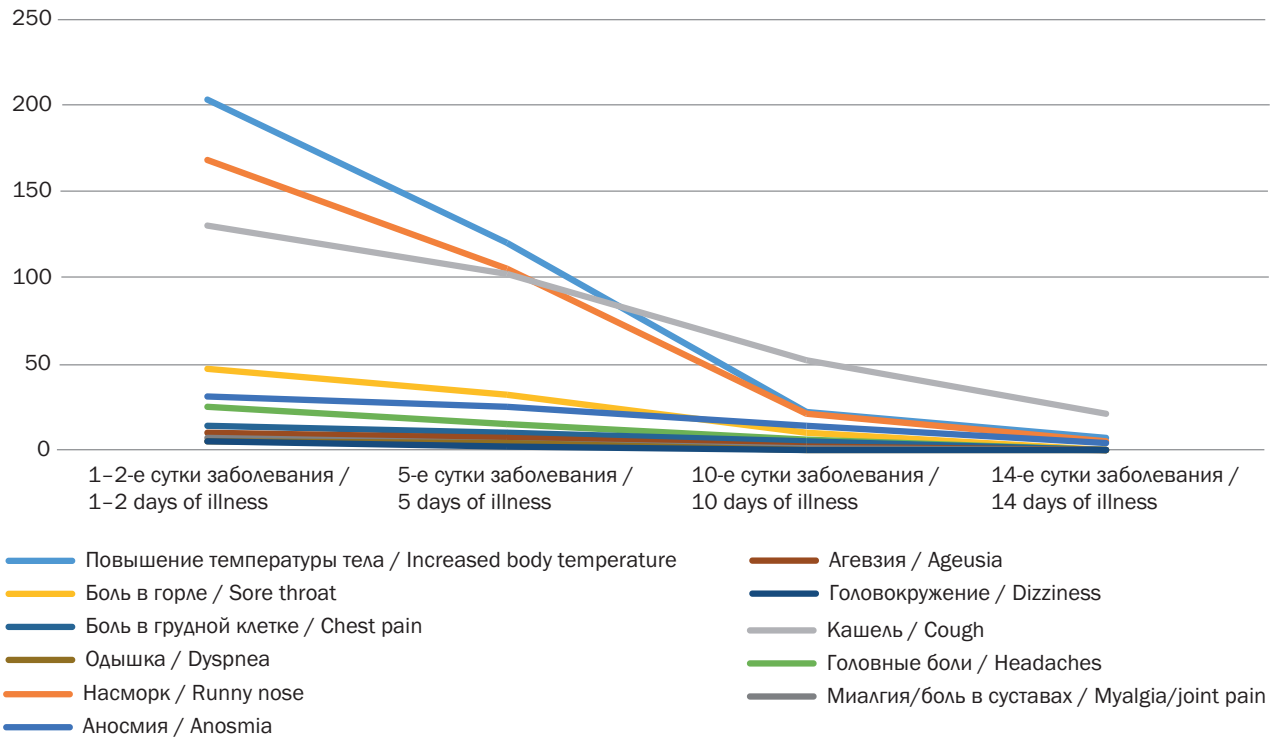

Fig. 3. Dynamics of acute new coronavirus infection in children

Рис. 3. Динамика заболевания острой новой коронавирусной инфекции у детей

Table 6. Dynamics of gastrointestinal complaints in examined patients

Таблица 6. Динамика гастроэнтерологических жалоб у обследованных пациентов

Симптомы / Symptoms	**Этапы наблюдения / Stages of observation**		**p**
	острая новая коронавирусная инфекция / acute novel coronavirus infection (n/%)	**14-е сутки заболевания (выздоровление) / 14th day of illness (recovery) (n/%)**	
Боли в животе / Abdominal pain	36 (13,3%)	18 (6,7%)	p_{1-2}=0,041
Тошнота / Nausea	16 (5,9%)	4 (1,5%)	p_{1-2}=0,016
Рвота / Vomition	29 (10,7%)	7 (2,6%)	<0,001
Жидкий стул / Loose stools	30 (11,1%)	7 (2,6%)	p_{1-2}=0,002

There was a significant reduction of most symptoms by the 10th day of observation and their disappearance on the 14th day. Cough persisted for the longest time.

New coronavirus infection proceeds in children in most cases in the form of typical acute respiratory viral infection of mild to moderate severity, with resolution of symptoms by the 14th day of the disease. The frequency of pneumonia among 270 examined patients amounted to 28,14% (76 children), the most significant number of pneumonias was found in children of group 4 (p=0,013), in them cough was noted most often.

Gastroenterological complaints were evaluated at the beginning of the disease and at the time of recovery (day 14). The dynamics of gastroenterological complaints in all 270 patients included in the study is presented in Table 6.

Analysis of these complaints shows that the frequency of vomiting, which can also be regarded as a manifestation of intoxication, significantly decreases by the time of recovery. The frequency of other gastroenterological complaints also decreases significantly by the time of recovery.

CONCLUSION

Thus, the leading complaints in children with confirmed new coronavirus infection were initially respiratory complaints, which did not allow distinguishing this disease from trivial acute respiratory viral infection. The frequency of gastroenterologic complaints (abdominal pain, nausea, vomiting, liquid stools) had a maximum occurrence of 16.4%. Age differences in the frequency of such subjective complaints as chest pain, sore throat, and nausea can be associated with the age-specific features of perception and evaluation of these symptoms in young children.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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WISKOTT–ALDRITCH SYNDROME (A CASE FROM PRACTICE): ALLOGENEIC BONE MARROW TRANSPLANTATION

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ABSTRACT. The article presents the results of our own clinical observation of a case of Wiskott-Aldrich syndrome, a combined primary immunodeficiency characterized by an X-linked recessive type of inheritance and manifested in a third of patients by a triad: recurrent microbial-inflammatory diseases, eczema (atopic dermatitis) and bleeding due to thrombocytopenia and platelet dysfunction. The disease occurs only in males and accounts for approximately 3% of all primary immunodeficiencies. In the given clinical example, the patient's diagnosis is based on a typical clinical picture (eczema, thrombocytopenia, immunodeficiency) and confirmed by the method of molecular genetic diagnostics. In the presented clinical example, it is relevant to describe the stages of therapy for a patient who, despite the high risk of life-threatening complications, ended with an unrelated allogeneic hematopoietic stem cell transplant from a fully compatible unrelated donor. During the follow-up of the child, it was found that, despite all the possible risks of complications, satisfactory functioning of the transplant was achieved with the restoration of platelet hematopoiesis. The post-transplant period, complications, therapy, and recommendations are described. The study of the presented clinical example will help to increase the effectiveness of early diagnosis of Wiskott–Aldrich syndrome and timely develop the correct treatment plan for the patient.

KEYWORDS: *child, Wiskott–Aldrich syndrome, thrombocytopenia, allogeneic unrelated bone marrow transplantation, complications, therapy, recommendations*

СИНДРОМ ВИСКОТТА–ОЛДРИЧА (СЛУЧАЙ ИЗ ПРАКТИКИ): АЛЛОГЕННАЯ ТРАНСПЛАНТАЦИЯ КОСТНОГО МОЗГА

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РЕЗЮМЕ. В статье представлены результаты собственного клинического наблюдения случая синдрома Вискотта–Олдрича — комбинированного первичного иммунодефицита, который характеризуется Х-сцепленным рецессивным типом наследования, и у трети больных проявляется триадой: рецидивирующими микробно-воспалительными заболеваниями, экземой (атопическим дерматитом) и кровотечениями, обусловленными тромбоцитопенией и дисфункцией тромбоцитов. Заболевание встречается только у лиц мужского пола и составляет приблизительно 3% всех первичных иммунодефицитов. В приведенном клиническом примере диагноз пациенту установлен на основании типичной клинической картины (экзема, тромбоцитопения, иммунодефицит) и подтвержден методом молекулярно-генетической диагностики. В представленном клиническом примере актуальным является описание этапности проведения терапии пациенту, которая, несмотря на высокий риск развития жизнеугрожающих осложнений, завершилась проведением неродственной аллогенной трансплантации гемопоэтических стволовых клеток от полностью совместимого неродственного донора. В ходе последующего наблюдения за ребенком было установлено, что, несмотря на все возможные риски развития осложнений, было достигнуто удовлетворительное функционирование трансплантата с восстановлением кроветворения по тромбоцитарному ростку. Описаны посттрансплантационный период, осложнения, проведенная терапия и рекомендации. Изучение представленного клинического примера поможет повысить эффективность ранней диагностики синдрома Вискотта–Олдрича и своевременно выстроить правильный план лечения пациента.

КЛЮЧЕВЫЕ СЛОВА: *ребенок, синдром Вискотта–Олдрича, тромбоцитопения, аллогенная неродственная трансплантация костного мозга, осложнения, терапия, рекомендации*

Wiskott–Aldrich syndrome (WAS) is a combined primary immunodeficiency characterized by X-linked recessive inheritance. In one third of patients manifests with the triad of recurrent microbial inflammatory diseases, eczema (atopic dermatitis) and bleeding due to thrombocytopenia and platelet dysfunction [1, 2]. The disease occurs only in male individuals. Female individuals do not suffer from this pathology, but can transmit the defective gene to the next generation. The gene responsible for the development of the disease (WAS-gene) is located on the short arm of the X chromosome Chr.11.22 and consists of 12 exons encoding 502 amino acids [3].

According to the literature, the incidence of boys born with WAS is 1 in 250,000 live births without ethnic or geographic predominance, which is approximately 3% of all primary immunodeficiencies [3, 4].

In WAS, WAS-protein (WASP) synthesis is reduced or not produced at all. The functions of this protein have not been fully understood to date. However, it has been found to play a key role in actin protein polymerization and cytoskeleton formation. WASP is expressed only in nucleus-containing cells of the hematopoietic system and is of exceptional importance for signal transduction from cell surface receptors to the actin cytoskeleton, which is dynamically regulated by it. Defects in the formation of all cellular structures, the formation of which depends on the cytoskeletal reorganization of actin filaments, are observed when WASP synthesis is reduced. This results in impaired function of cells that normally express WASP (leukocytes and platelets). It has been found that the concentration of myosin, which also takes part in the formation of the cytoskeleton, is significantly reduced in platelets of patients with WAS [5].

The full function of actin cytoskeleton plays an important role at the stage of platelet production by megakaryocytes in bone marrow (BM), as well as for the realization of their adhesive, aggregation and other functions. Thrombocytopenia and decreased platelet size is a consistent laboratory sign of WAS. Usually the platelet count varies from 30 to 140 G/L, but periodically decreases to 10–30 G/L. In the BM punctate of patients, the absence of megakaryocytes is determined. The clinical picture of the disease is characterized by the development of hemorrhagic syndrome, which intensifies against the background of infectious process, chronic posthemorrhagic anemia and enlargement of the spleen [5, 6].

B- and T-lymphocyte synthesis, formation of immune synapses of T-lymphocytes, chemotaxis of WASP-deficient leukocytes, cytolytic activity of NK cells, IgG-mediated phagocytosis and, consequently, antigen presentation are impaired in patients with WAS. These changes lead to the development of recurrent bacterial, fungal and viral infections [3, 6].

In the first year of life, the presence of WAS in a child can be suggested by a characteristic triad of clinical symptoms: bleeding, eczema, and recurrent infections [1, 7]. The disease usually debuts with bloody diarrhea, petechial rash on the skin, oral mucous membranes, prolonged healing of the umbilical wound, and eczema. The classical triad usually develops in only one third of children with WAS, and in the remaining cases, the manifestations may be in the form of thrombocytopenia or infectious diseases, or isolated eczema [8]. There is an increased incidence of autoimmune diseases such as hemolytic anemia, vasculitis, glomerulonephritis, and inflammatory bowel disease in patients with WAS [9].

The only curative method of treating WAS is hematopoietic stem cell transplantation (HSCT) from an HLA-compatible related or unrelated donor. The best results of transplantation are noted in patients in the first two years of life in the absence of severe infectious and/or autoimmune complications [1, 2, 6]. Introduction of hematopoietic stem cells (HSC) from a donor to a recipient is performed for partial or complete replacement of hematopoiesis after cytostatic and/or radiation therapy [8, 10].

Depending on the donor, HSC are divided into autologous (auto-HSCT) — the recipient is the donor of HSC, and allogeneic (allo-HSCT) — HSC are obtained from related and unrelated donors. The main sources of HSC for transplantation are BM cells (HSC content 1–3%) and peripheral blood stem cells (PBSC) — HSC content in norm is 0,01–0,1%, after mobilization it is up to 2%. Less often the source of HSC is umbilical cord blood — the content of HSC at the 38th week of pregnancy is about 1%. The qualitative composition of the transplant depends on the source of its obtaining. Each source has its advantages and disadvantages, which are considered in the context of the nature of the disease, HLA-system gene compatibility, age, weight of the recipient and donor when choosing a transplant [10–12].

It should be noted that selection of an unrelated donor with optimal characteristics is impossible for 30%

of patients due to allelic polymorphism of HLA genes. Reduced degree of HLA-compatibility creates additional risks of severe complications, namely, it increases the probability of graft-versus-host reaction (GVHR) [10]. When making a decision on HSCT, it is necessary to analyze the correlation between the risk of death, development of severe complications associated with the disease, and the risk of HSCT procedure [12–14].

The success of therapy also depends on such significant factors as conditioning regimen, GVHR prophylaxis, concomitant therapy, the status of the underlying disease and clinical features of its course [11, 15, 16].

Aim. To study clinical manifestations of WAS and methods of its treatment on the example of a particular patient.

We present **a clinical case of our own observation** of a patient with WAS.

The boy K., 5 months old, was in the pediatric department of the City Children's Clinical Hospital No. 1 in Donetsk.

He was admitted with his parents' complaints about changes in clinical blood analysis in the form of moderate anemia and thrombocytopenia.

Anamnesis. The child was born from VIII pregnancy at 39 weeks gestation. The pregnancy proceeded against the background of edema of pregnancy, chronic cytomegalovirus infection (CMVI), genetic thrombophilia. I pregnancy ended in childbirth — the boy died at the age of 3 months, according to the mother's words, the child was diagnosed with leukemia (a child from the first marriage). II, III, IV pregnancies ended with medical abortions. V pregnancy ended in childbirth — the boy died at the age of 7 months (child from the second marriage). VI pregnancy ended in childbirth — the girl is healthy (child from the third marriage). VII pregnancy ended in childbirth — boy died at the age of 3 months, the child was diagnosed with congenital CMVI, pneumocystis pneumonia (child from the fourth marriage). These labor was V, term, normal; Apgar score was 7/8 points. The baby's weight at birth was 4300 g.

By three months of life, the child had twice suffered intestinal infection caused by *Klebsiella pneumoniae*. Examination in the department revealed thrombocytopenia — 50 G/L, anemia of average severity. Due to the revealed changes in blood tests he was hospitalized in the oncohematology department of the State Institution "Institute of Emergency and Reconstructive Surgery named after V.K. Gusak". with the diagnosis: acute CMVI, active phase, primary immunodeficiency, severe anemia, thrombocytopenia.

A positive titer of IgM and IgG to cytomegalovirus was detected, a BM puncture was performed. Myelogram showed the following changes: BM punctate is small cellular, there are no BM elements (megakaryocytic and erythrocytic sprout). It is possible overdilution with peripheral blood. It was recommended to repeat the BM puncture to clarify the diagnosis. Normal human immunoglobulin was administered to the child in the department. The child was consulted by an infectious disease specialist and diagnosed with congenital CMVI, manifest generalized form (hematological, hepatic) against the background of congenital immunodeficiency. Then the child was transferred to the intensive care unit of City Children's Clinical Hospital No. 1 in Donetsk for treatment of CMVI. In the ward he received human anti-cytomegalovirus immunoglobulin.

Due to the severity of the anemic syndrome, thrombocytopenia, neutropenia, lack of positive dynamics from the therapy, the child was repeatedly transferred to the oncohematology department of the "Institute of Emergency and Reconstructive Surgery named after V.K. Gusak". A repeated BM puncture was performed: BM preparations were cellular, erythroid sprout was of normoblast type. Blood system diseases were excluded. The child underwent transfusion of thromboconcentrate, infusion of human anti-cytomegalovirus immunoglobulin. For further treatment and observation, the child was transferred to the pediatric department of City Children's Clinical Hospital No. 1 in Donetsk.

At the time of our examination, the general condition of the child was severe. Body temperature was 36.7 °C, heart rate was 111 per minute, respiratory rate was 26 per minute. The weight of the child was 9580 g. Consciousness was preserved, active. Skin was pale. There were traces of intravenous injections on the skin of temples, elbow bends, wrist joints. On the skin of the face, trunk there were elements of papular rash, areas of desquamation, single elements of petechial rash on the trunk. Visible mucous membranes were pale pink, normally moist. Above the lungs percussion there was clear pulmonary sound.During the auscultation we heard puerile respiration. Heart tones were muffled, rhythmic. The abdomen was not enlarged in volume, accessible to palpation. The liver protrudes 2 cm from under the edge of the rib arch, the spleen was 2.5 cm

below the edge of the rib arch. Stool was 1–2 times a day, mushy. Urination was not disturbed.

The child was examined.

Anemia of varying severity, neutropenia and thrombocytopenia (23–95 g/L) were registered in the clinical blood analysis throughout the observation.

Blood biochemical analysis parameters were within the age normal range.

The determination of CD4 lymphocyte subpopulation was carried out — 1628 cells (42,9%), which corresponds to the age norm.

Ultrasound examination of abdominal cavity organs was without pathology.

Neurosonogram — there was slight ventriculodilation, lenticulostriary vasculopathy.

Echocardiography (EchoCG) — there was minimal tricuspidal and pulmonal regurgitation, aberrant chorda in the left ventricular cavity.

On X-ray examination of chest organs there was no pathology.

The patient was consulted by otorhinolaryngologist, ophthalmologist, neurologist, allergologist, immunologist — recommendations for further examination and treatment were given.

Geneticist consultation: the child was diagnosed with WAS. For technical reasons, specific molecular genetic diagnosis of this syndrome could not be realized. Medical and genetic counseling of the family was carried out.

In the course of telemedicine consultation with the staff of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology of the Russian Ministry of Health a conclusion was obtained. According to the submitted documents, taking into account the aggravated family history (death of male children in infancy), clinical symptoms, and laboratory changes, the child is likely to be diagnosed with primary immunodeficiency syndrome. Molecular genetic examination "Immunologic Panel" and TREC/KREC determination were recommended. Blood was collected for this study, the blood sample was sent to the immunology department of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology of the Russian Ministry of Health. After receiving the results of genetic studies, a telemedicine consultation with the staff of this institution was repeated. The following conclusion was received: according to the data of the genetic examination, the patient was confirmed to have primary immunodeficiency: WAS. The only curative method of treatment is HSCT from an unrelated or haploidentical donor.

A telemedicine consultation with the staff of the Russian Children's Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Health of Russia was conducted. Final diagnosis based on the results of the consultation: primary immunodeficiency. WAS. Congenital CMVI. Anemia of mild severity. Dysplastic cardiopathy. It was recommended to continue the prescribed therapy, to conduct HLA-typing of the child, parents, to start searching for a compatible BM donor with subsequent BM transplantation (HSC). To correct thrombocytopenia it is reasonable to prescribe romiplostim or eltrombopag. Platelet transfusion is indicated only in case of bleeding.

In the department, the child received valganciclovir, co-trimoxazole, fluconazole, colecalciferol, thromboconcentrate transfusions, normal human immunoglobulin, and iron preparations.

Repeated telemedicine consultation was carried out at the Russian Children's Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education "N.I. Pirogov Russian National Research Medical University" of the Ministry of Health of Russia. The diagnosis remained the same. Conclusion: haploidentical BM transplantation in a patient with this diagnosis carries a very high risk of life-threatening complications, which makes its feasibility doubtful. The search for an unrelated compatible BM donor was recommended, and the current treatment (romiplostim, normal human immunoglobulin, valganciclovir, co-trimoxazole) was continued.

The child was started on romiplostim therapy — 8 injections.

At the age of 1 year 6 months, the patient was admitted to the Clinic of the R.M. Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantology in satisfactory condition for examination and decision on allogeneic BM transplantation. At the time of admission the hemogram were anemia of medium severity, thrombocytopenia of IV degree. Due to severe thrombocytopenia the patient was on romiplostim therapy, which was suspended due to the lack of the drug. Infectious complications were represented by congenital CMVI, generalized form. He received therapy with vanganciclovir. Taking into account the nature and course of the disease, the patient

was shown to perform allo-HSCT. A search for a donor in the Russian registry was activated.

A fully compatible unrelated donor was found. The child was hospitalized for allo-HSCT. The conditioning regimen of nonmyeloablative FluTreoThio was tolerated relatively satisfactorily. Unrelated allo-HSCT from a fully compatible donor was performed. The graft source was BM. GVHR prophylaxis, drug administration was tolerated without immediate complications.

The early post-transplantation period was complicated by the course of gastrointestinal tract mucositis of II-III degree. From day 6 he received partial parenteral nutrition. The first wave of febrile neutropenia — from day 9 with response to empirical antibacterial therapy, apyrexia was achieved by day 11.

Infectious complications — pulmonary aspergillosis. Against the background of etiotropic therapy, positive dynamics was achieved in the form of regression of previously existing foci according to computed tomography.

Recovery of donor hematopoiesis by the platelet sprout (more than 20 thousand/μL) was recorded by day 14. Platelets more than 50 thousand/μL were recovered by the 16th day and more than 100 thousand/μL by the 21st day. The recovery of hematopoiesis in the leukocytic sprout was registered on the 22nd day, in neutrophils it was registered on the 23rd day.

The graft engrafted independently without stimulation with granulocyte colony-stimulating factor on the 25th day, chimerism was complete donor.

Therapy of acute grade I GVHR (grade II skin) produced a complete response to systemic glucocorticosteroid therapy from day 25.

The graft functions satisfactorily, chimerism is full donor, hematransfusion-independent. Basal immunostimulating therapy was performed: tacrolimus, mycophenolate mofetil.

The patient was diagnosed with the following clinical diagnosis.

Primary diagnosis. Primary immunodeficiency. WAS (mutation in WAS gene in homozygous state). Allogeneic unrelated BM transplantation.

Complication. Bilateral multisegmental pneumonia of mixed etiology (CMVI, *Actinomyces* spp., *Streptococcus salivaris*). Probable invasive pulmonary aspergillosis. Postcytostatic pancytopenia (severe anemia, grade IV thrombocytopenia, grade IV neutropenia). GI mucositis of II–III degree. Febrile neutropenia. Acute GVHR grade I (skin grade II), complete response. Colonization of the GI tract with *Klebsiella pneumoniae*, *Esherichia coli*, *Candida lusitaniae*. Colonization of the pharynx with *Str. viridans group*, *Str. epidermidis*. Urinary tract infection, asymptomatic bacteriuria (*Str. epidermidis*, *Enterocccus faecalis*). Reactivation of CMVI, chronic course.

Secondary diagnosis. Presence of other transplanted organs and tissues.

Therapy given: platelet concentrate, normal human immunoglobulin; chemotherapy: fludarabine, treosulfan, thiotepa; immunosuppressive therapy: tacrolimus, mycophenolate mofetil, methylprednisolone; concomitant therapy: Omeprazole, ciprofloxacin, acyclovir, voriconazole, co-trimoxazole, pancreatin in microgranules, cefoperazone with sulbactam, ganciclovir, allopurinol, fluconazole, paracetomol.

The patient was given recommendations:

- observation of pediatrician, hematologist, immunologist;
- continue taking tacrolimus, mycophenolate mofetil, folic acid, valganciclovir, variconazole, cotrimoxazole, pancreatin, omeprazole; if the IgG level decreases less than 4.0 g/l, it is recommended to carry out replacement transfusion with normal human immunoglobulin;
- control of analyzes: clinical blood analysis, biochemical blood analysis, urinalysis, quantitative polymerase chain reaction to cytomegalovirus, Epstein-Barr virus, herpes virus, determination of IgG level;
- physical therapy, rehabilitation, high-calorie, high-protein, hypoallergenic diet;
- immunomodulators and intramuscular injections are contraindicated;
- medical withdrawal from vaccination;
- repeated hospitalization at the R.M. Gorbacheva Research Institute to control the therapy.

Conclusion. Thus, the peculiarity of this case is the presence in the patient of the classical triad of symptoms characteristic of WAS (eczema, thrombocytopenia, immunodeficiency), with confirmation of the diagnosis by molecular genetic study. It is indicated that during the treatment of the child, combined therapy of infectious manifestations of this primary immunodeficiency, eczema, substitution therapy with intravenous immunoglobulin and thrombocytopenia allowed to achieve only a temporary positive effect. In the

presented clinical example it is relevant to describe the stages of therapy of the patient, which, despite the high risk of life-threatening complications development, ended with allo-HSCT from a fully compatible unrelated donor. During the follow-up of the child it was found that despite all possible risks of complications development, satisfactory functioning of the transplant with restoration of hematopoiesis by the platelet sprout was achieved. The study of the presented clinical case will help to improve the efficiency of early diagnosis of WAS and timely build a proper treatment plan for the patient.

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

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CLINICAL CASE OF SEVERE POISONING WITH PARACETAMOL IN A CHILD

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ABSTRACT. Paracetamol poisoning is an urgent problem in toxicology due to a significant increase in the number of cases worldwide, and the use of paracetamol for suicidal purposes in many countries occupies a leading position in the structure of drug suicides. ***The aim of the work*** is to review a clinical case of paracetamol poisoning. ***Materials and methods:*** paracetamol poisoning in a 17-year-old child at a dose of 600 mg/kg. Intensive care: antidote N-acetylcysteine, hepatoprotection ademetionine, ultrahemodiafiltration, transfusion of fresh frozen plasma. A feature of this case is not only liver damage, but also kidney damage. Intensive care is aimed at cleansing the body of hepatolysis products and uremic toxins. It was possible to avoid hepatocellular damage requiring liver transplantation and renal damage requiring chronic hemodialysis.

KEYWORDS: *paracetamol, poisoning, children*

КЛИНИЧЕСКИЙ СЛУЧАЙ ТЯЖЕЛОГО ОТРАВЛЕНИЯ ПАРАЦЕТАМОЛОМ У РЕБЕНКА

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РЕЗЮМЕ. В настоящее время отравление парацетамолом является актуальной проблемой токсикологии в связи со значительным увеличением числа случаев во всем мире, а применение парацетамола в суицидальных целях во многих странах занимает лидирующие позиции в структуре медикаментозных сиуцидов. ***Цель работы*** – обзор клинического случая отравления парацетамолом. ***Материалы и методы:*** отравление парацетамолом у ребенка 17 лет в дозе 600 мг/кг. Интенсивная терапия: антидот N-ацетилцистеин, гепатопротекция адеметионин, ультрагемодиафильтрация, трансфузия свежезамороженной плазмы. Особенностью данного случая является не только поражение печени, но и почек. Интенсивная терапия направлена на очищение организма от продуктов гепатолиза и уремических токсинов. Удалось избежать необратимого печеночно-клеточного повреждения, требующего трансплантации печени, и необратимого почечного повреждения, требующего проведения хронического гемодиализа.

КЛЮЧЕВЫЕ СЛОВА: *парацетамол, отравление, дети*

INTRODUCTION

Paracetamol is one of the most widely used drugs worldwide for its analgesic and antipyretic properties and is generally safe when taken in the recommended therapeutic dose.

Reports of paracetamol poisoning are frequent and have been studied in many countries. The epidemiological significance of paracetamol poisoning is due to the widespread use and wide availability of the drug. Paracetamol is used as an analgesic and antipyretic. In the Russian Federation (RF) traditionally has the greatest use in children's practice, but in recent years due to the introduction of new dosage forms has become more widely used in adults. For example, the use of paracetamol in oncology is included in the standards of treatment of chronic pain, it is also used in therapy and rheumatology, and in surgical practice, including in combination with opioid analgesics [1].

Paracetamol poisoning is currently an urgent problem of toxicology due to a significant increase in the number of cases worldwide. Paracetamol poisoning in the USA and Australia is the most common cause of severe acute liver injury requiring transplantation [2]. In European countries, this figure averages 20%. In Ireland it is 52%, in Great Britain it is 28%, in France it is 18%, in the Netherlands it is 8%, and in Italy it is 1% [1]. In the Russian Federation, according to the data of 2008, the specific weight of paracetamol poisonings was only 0.67% among all poisonings, but in recent years has increased significantly due to the emergence in the domestic pharmaceutical market a large number of different dosage forms containing paracetamol, including long-acting, under different trade names [3]. At the same time, up to 60% of overdoses were also deliberate self-poisoning.

It should be noted that the use of paracetamol for suicidal purposes in many countries takes the leading position in the structure of medication suicides: in the UK – 44.9%, in New Zealand – 37.6%, in Ireland – 30%, in Canada – 30%, in Australia – 28%, in the USA – 10.9% [3].

The toxic dose of paracetamol is 7.5 g in adults and 150 mg/kg in children [4]. A number of authors point out that hepatotoxic effect is possible already when taking the drug at a dose of 4–5 g in adults or 125 mg/kg in children with concomitant liver diseases, constant intake of drugs, especially those that are inducers of cytochrome P450 (barbiturates, isoniazid, rifampicin, diphenin, etc.), dietary supplements, anorexia, etc. [5].

The toxicity of paracetamol is related to the action of its active metabolite N-acetyl-p-benzoquinonimine (NAPQI) formed by the cytochrome P450 system in the liver. Formed in small amounts, it is detoxified by reduced glutathione (GSH). When a massive dose of paracetamol is taken, GSH is consumed and its regeneration step is limited by cysteine stores. As a result, NAPQI forms covalent bonds with macromolecules of hepatocyte membranes, activating free-radical processes and leading to hepatocyte necrosis [6].

The antidote is N-acetylcysteine, which reduces the toxic effects of NAPQI by restoring cysteine reserves.

AIM

Review of a clinical case of paracetamol poisoning at a dose of 600 mg/kg.

CLINICAL CASE

A 17-year-old child was undergoing treatment in the anesthesiology and resuscitation department of the Children's Republican Clinical Hospital of Ulan-Ude.

The girl was admitted to the hospital for emergency indications. From the anamnesis it is known that she drank 60 tablets of paracetamol 500 mg for suicidal purposes, the next day she was bothered by nausea and vomiting, she sought medical help 37.5 hours after taking the drug. Thus, the taken dose of paracetamol amounted to 30 g (600 mg/kg).

There were complaints of nausea, weakness, lethargy, abdominal pain. Consciousness was clear. Skin was pale pink, clean, warm. Breathing was independent, adequate. Hemodynamics was compensated, with a tendency to hypotension. Heart tones were muffled, rhythmic. Heart rate (HR) was 83 per minute. Blood pressure (BP) was 104/59 mm Hg. The abdomen was of normal shape, soft, not swollen, accessible to deep palpation, moderately painful at palpation in the upper parts, more on the right side. The liver was on the edge of the rib arch. Diuresis was preserved, urine was light yellow.

Laboratory data at the time of admission: Leukocytosis/neutrophilosis (14.9/12.1×10^9/L), elevation of alanine and asparagine transaminases of 1713 U/L and 1039 U/L, respectively, hyperbilirubinemia up to 83.1 μm/L, elevation of lactate dehydrogenase up to 10505 U/L, gamma-glutamyltransferase — 50 U/L, expressed hypocoagulation on coagulogram (activated partial thromboplastin time (APTT) — 30.8 s, fibrinogen — 4.315 g/l, prothrombin time — 27.9 s, thrombin time — 16.1 s, prothrombin index — 19.9%, international normalized ratio (INR) — 2.94).

On admission, toxic liver damage, proceeding by the type of acute hepatitis, liver-cell failure was noted. Potential hepatotoxicity can be assessed by plasma concentration of paracetamol using the Ramek–Mathew 150 nomogram [7]. In our case, the concentration of paracetamol was not determined due to the lack of necessary equipment. The severity of liver damage was assessed by the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and INR [7].

Starting intensive therapy.

1. Infusion therapy according to the formula 4:2:1 = 2615.0 ml/day. Polyionic crystalloid solutions and solutions containing meglumine sodium succinate were used.

2. Antidote therapy — Acetylcysteine 150 mg/kg.

3. Enterosorbent Enterosgel per os.

4. Hepatoprotector Ademetionine 400 mg × 2 times daily intravenously.

5. Proton pump inhibitors: Omeprazole 40 mg × × 2 times a day intravenously.

Taking into account the negative dynamics during the first day in the form of increasing hepatic cellular insufficiency, the consilium decided to conduct a session of continuous venous-venous ultrahemodiafiltration with parameters: dialysate flow 2000 ml/h, substrate flow 2000 ml/h, blood flow 100 ml/min,

Table 1. Biochemical blood parameters

Таблица 1. Биохимические показатели крови

Показатель / Parameter	**При поступлении / On admission**	**1-е сутки / day**	**2-е сутки / day**	**3-и сутки / day**	**4-е сутки / day**	**5-е сутки / day**	**6-е сутки / day**
Билирубин, мкмоль/л / Bilirubin, μmol/l	83,1	63	78,3	72,8	54,9	18	18,6
АСТ, ЕД/л / AST, U/l	1039	2154	4900	2076	321	102,6	255
АЛТ, ЕД/л / ALT, U/l	1713	2745	2370	6684	3099	1843	1520
Общий белок, г/л / Total protein, g/l	67,6	57	55,9	51,9	52,2	40	49
Глюкоза, ммоль/л / Glucose, mmol/l	6,9	3,8	10,8	4,5	4,1	4,0	4,89
Лактатдегидрогеназа, ЕД/л / Lactate dehydrogenase, U/l	10505	400	42	1176	–	402	367
Креатинфосфокиназа, ЕД/л / Creatine phosphokinase, U/l	89	125	150	75	–	69	80
Международное нормализованное отношение / International normalized ratio	2,94	5,5	3,72	1,8	1,4	1,19	1,15
Активированное частичное тромбопластиновое время, с / Activated partial thromboplastin time, s	30,8	49,3	36,3	27,6	25,5	25,7	–
Фибриноген, г/л / Fibrinogen, g/l	4,31	1,1	1,14	1,19	1,5	1,8	–
Протромбиновое время, с / Prothrombin time, s	27,9	50,6	34,8	17,6	12	11,6	–
Тромбиновое время, с / Thrombin time, s	16,1	21,3	24,7	23,9	25,8	19	–
Протромбиновый индекс, % / Prothrombin index, %	19,9	9,3	14,8	36,7	68,4	74,4	–

Table 2. Renal function indicators

Таблица 2. Показатели функции почек

Показатель / Parameter	При поступлении / On admission	1-е сутки/ day	2-е сутки/ day	3-и сутки/ day	4-е сутки/ day	5-е сутки/ day	6-е сутки/ day
Диурез, мл/кг/ч / Diuresis, ml/kg/h	сохранен	0,2	0,15	0,3	0,3	1,1	2,6
Мочевина, ммоль/л / Urea, mmol/l	5,4	4,63	3,0	4,2	3,8	9,09	3,55
Креатинин, мкмоль/л / Creatinine, μmol/l	81,4	135	124	100	246	428	84

ultrafiltration 30 ml/h. The levels of alanine and asparagine transaminases increased 2745 U/L and 2154 U/L, respectively.

During the first 24 hours there was an increase in renal failure, decrease in diuresis to 0.2 ml/kg per hour with urea and creatinine levels remaining in the area of normal values. A session of continuous veno-venous ultrahemodiafiltration was continued. Taking into account oliguria, renal ultrasound data (decreased blood flow rate in the right kidney), the ultrafiltration rate was stepwise increased from 70.0 to 200.0 ml/kg per hour. Furosemide was prescribed.

Table 1 shows the dynamics of blood biochemical parameters during the first six days of treatment in the intensive care unit (ICU).

Antidote therapy with acetylcysteine (ACC) was performed according to the Clinical Recommendations (protocol) for emergency medical care in acute poisoning in children according to a 21-hour scheme in three stages: Stage 1 — saturating dose of ACC in the first 60 minutes (150 mg/kg); Stage 2 — maintenance dose of 50 mg/kg for 4 hours; Stage 3 — 100 mg/kg for 16 hours. When blood levels of ALT and AST were found to be elevated more than 2-fold again, intravenous administration of ACC was continued according to the 21-hour protocol [8]. The risk of liver failure increases when acetylcysteine therapy is started later than 10 hours from the toxic dose, and administration of acetylcysteine later than 24 hours from the time of poisoning is unable to prevent liver damage, but implemented from the 36th hour from poisoning can limit the severity of toxic hepatitis [9]. It should also be noted that the use of acetylcysteine is appropriate even in late stages in all poisonings characterized by liver damage [10].

By the end of the first day after admission to the hospital, oliguria was noted in the child. Table 2 shows renal function parameters during the first six days of treatment in ICU.

At renal ultrasound, blood flow velocity indices in the renal artery trunk, interlobular and arch arteries were within normal limits (to the lower limit of normal) on both sides. Moderate decrease in blood flow in segmental arteries on both sides with increased peripheral resistance index on the right side.

Ultrahemodiafiltration was canceled on the fifth day, diuresis was restored, urea and creatinine levels normalized on the sixth day.

Despite the absence of clinically pronounced hemorrhagic syndrome, three transfusions of quarantined fresh frozen plasma were performed in the first three days on the basis of laboratory confirmation of hemostasis disorders (Table 1).

Partial enteral nutrition was started from the second day of treatment in the ICU with gradual expansion to the full volume by the fourth day (table No. 5).

In the hospital the child underwent the following instrumental examinations: ultrasound of the abdominal cavity and urinary system (separately with Doppler study of the renal vessels), electrocardiography, magnetic resonance imaging of the abdomen, echocardiography with color mapping, radiography to visualize the venous catheter.

On the seventh day the child was transferred to the pediatric department. Later, with positive dynamics, he was discharged with recommendations for dispensary registration of a psychologist, nephrologist, and gastroenterologist at the district polyclinic.

CONCLUSION

This clinical observation presents the multifaceted nature of damage in paracetamol poisoning. The peculiarity of this case is not only liver but also kidney

damage. Aggravating factors are the high dose (600 mg/kg) and late medical attention — more than 36 hours after taking the drug. Intensive therapy is aimed at cleansing the body of hepatolysis products and uremic toxins. Irreversible hepatic cellular damage requiring liver transplantation and irreversible renal damage requiring chronic hemodialysis were avoided. The absence of severe hypocoagulation with hemorrhagic syndrome allowed invasive procedures to be performed without complications. The use of antidote therapy with N-acetylcysteine in children is regulated in the 2015 clinical guidelines.

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.

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DRAFT CLINICAL RECOMMENDATIONS FOR NEONATOLOGISTS AND PEDIATRICIANS ON THE MANAGEMENT OF NEWBORN CHILDREN SUFFERING FROM REGURGITATION / RUMINATION (FOR DISCUSSION BY SPECIALISTS)

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ABSTRACT. The practical recommendations are intended to optimize the tactics of managing newborns with regurgitation and are offered for use by neonatologists, pediatricians, gastroenterologists working in the outpatient healthcare of the Russian Federation, as well as all specialists who are interested in neonatology and clinical gastroenterology. These practical recommendations are offered for public discussion and are posted in full on the website of the Russian Society of Neonatologists: https://neonatology.pro.

KEYWORDS: *newborns, regurgitation, rumination, diagnostics, treatment, practical recommendations, clinical guidelines*

ПРОЕКТ КЛИНИЧЕСКИХ РЕКОМЕНДАЦИЙ ДЛЯ НЕОНАТОЛОГОВ И ПЕДИАТРОВ ПО ВЕДЕНИЮ НОВОРОЖДЕННЫХ ДЕТЕЙ, СТРАДАЮЩИХ СРЫГИВАНИЕМ / РУМИНАЦИЕЙ (ДЛЯ ОБСУЖДЕНИЯ СПЕЦИАЛИСТАМИ)

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РЕЗЮМЕ. Практические рекомендации предназначены для оптимизации тактики ведения новорожденных со срыгиванием и предлагаются к использованию врачам-неонатологам, педиатрам, гастроэнтерологам, работающим в амбулаторном звене здравоохранения Российской Федерации, а также всем специалистам, кто проявляет интерес к неонатологии и клинической гастроэнтерологии. Настоящие практические рекомендации предлагаются к обсуждению общественности и в полном виде опубликованы на сайте Российского общества неонатологов: https://neonatology.pro.

КЛЮЧЕВЫЕ СЛОВА: *новорожденные, срыгивание, руминация, диагностика, лечение, практические рекомендации, клинические рекомендации*

DEFINITIONS

Rumination syndrome is a functional gastrointestinal (GI) disorder characterized by repeated, effortless regurgitation. It occurs when recently swallowed food enters the mouth followed by a new episode of chewing and then swallowing or removal of a food clump, which is usually tasteless but may be sour or bitter because it occurs a few minutes after eating. Rumination syndrome (RS) is often misdiagnosed as gastroesophageal reflux disease (GERD) or vomiting, leading to unnecessary testing and treatment [1–5].

Regurgitation is a symptom characteristic only for newborns and children of the first year of life. In regurgitation, gastric contents are thrown passively without tension of the abdominal press and diaphragm. Unlike vomiting, regurgitation is not accompanied by autonomic reactions. In most cases, RS and regurgitation are uncomplicated self-limiting conditions that spontaneously resolve by the age of 12–15 months, but despite this, they can cause significant discomfort for parents due to increased parental stress and potential impact on quality of life [1, 3, 4, 6].

Features of the disease coding according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision

P92.1 Regurgitation and rumination of newborn.

EPIDEMIOLOGY

The true prevalence of regurgitation in infants of the newborn period is unknown. Using the Rome IV criteria, taking into account age, ethnicity, birth weight, gestational age, and age of weaning, daily regurgitation occurs in infants with an incidence ranging from 10.5 to 86.9% [7–11]. When the Rome IV criteria are not met, the incidence of regurgitation is reported in almost 100% of newborns [12].

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the prevalence of RS, especially in newborns, is not studied because different diagnostic criteria are used for diagnosis depending on the clinical situation. According to some reports, it ranges from 0.8 to 10.6% in community samples [13–18].

ETIOLOGY AND PATHOGENESIS OF THE DISEASE

Regurgitation is physiological in nature and is related to the mechanism of sucking – it facilitates the expulsion of excess ingested air from the stomach. By the 6th month of life, the lower esophageal sphincter (LES) is complete, and symptoms of its dysfunction later in life may be considered as pathological.

Causes of regurgitation/ruminations in newborn infants [7, 19–28]:

1) high pressure in the abdominal cavity due to tight swaddling, constipation, increased gas formation, prolonged crying, violation of feeding technique (aerophagia), overfeeding;
2) syndrome of vegetovisceral disorders in cerebral ischemia (pylorospasm), GI dyskinesia, hereditary diseases associated with metabolic disorders;
3) low gestational age (<32 weeks);
4) low birth weight (<1.5 kg);
5) delivery by cesarean section;
6) early transfer to artificial feeding;
7) use of antibiotics in both mother and newborn;
8) inappropriate use of probiotics;
9) allergy (intolerance) to cow's milk;
10) duration of hospitalization of the newborn for more than 7 days;
11) harmful habits of the mother (including smoking history);
12) RS is characterized by emotional neglect (habitual style of interaction in the family, when parents do not notice and insufficiently respond to the emotions of children and their emotional needs) [29].

The high frequency of regurgitation in newborns and children of the first year of life is caused by the *peculiarities of the structure of the upper digestive tract* [7, 19]:

- the esophagus is wide, funnel-shaped, the expansion of the funnel is turned upwards;
- the muscular layer of the esophagus is poorly developed, anatomical constrictions are poorly expressed;

- the ligamentous apparatus is friable and delicate, the legs of the diaphragm loosely cover the esophagus;
- esophagus passes into the stomach at right angles;
- the stomach has a spherical shape;
- the pyloric section of the stomach is well developed, while the cardiac section is poorly expressed;
- there is practically no zone of increased pressure over the lower esophageal sphincter;
- there is immaturity of the nervous and humoral link of regulation of the sphincter apparatus and motility of the GI tract in the first years of life of the child.

The pathophysiology of rumination syndrome is not fully understood. The key mechanism may be an imperceptible postprandial contraction of the abdominal wall. Retrograde throwing of gastric contents into the oral cavity is realized due to the simultaneous combination of increased intra-abdominal pressure and negative intrathoracic pressure [15–18].

CLASSIFICATION

According to the Rome IV consensus, regurgitation/ruminations are classified as a "functional gastroduodenal disorder" [3]. According to the criteria adopted by the American Psychiatric Association in 2022 (DSM-5), regurgitation/ruminations are categorized under the term "feeding and eating disorder" [2].

CLINICAL PICTURE

The clinical picture of regurgitation/rumination is variable and nonspecific.

Characteristic symptoms of rumination disorder are regular regurgitation and repeated chewing of food. During regurgitation, children make peculiar movements: tense the muscles of the back and abdomen, arch their backs, throw their heads back and as if they were sucking or swallowing something. The most common parental complaint is frequent vomiting. The physical mechanism generating the regurgitation/ruminative phenomena depends on an involuntary process that changes the pressure in the abdomen and thorax accompanied by an esophageal-gastric junction [34].

The main clinical characteristics include [30]:

1) early postprandial regurgitation;
2) regurgitated material is effortlessly regurgitated similar to swallowed food;
3) regurgitated material is spit out or swallowed again.

Frequent regurgitation can lead to significant weight loss and dehydration. The severity of regurgitation syndrome, according to the recommendations of the ESPGHAN expert group, is assessed on a five-point scale (Table 1).

Table 1. Scale for assessing the intensity of regurgitation

Таблица 1. Шкала оценки интенсивности срыгиваний [35]

Количество баллов / Number of points	**Характеристика / Characteristic**
0	Отсутствие срыгиваний / No regurgitation
1	Более 5 срыгиваний в сутки объемом не более 3 мл / More than 5 regurgitations per day with a volume of no more than 3 ml
2	Более 5 срыгиваний в сутки объемом более 3 мл / More than 5 regurgitations per day with a volume of more than 3 ml
3	Более 5 срыгиваний в сутки объемом до половины объема одного кормления, не чаще чем в половине кормлений / More than 5 regurgitations per day in a volume of up to half the volume of one feeding, no more often than in half of the feedings
4	Срыгивания небольшого объема в течение 30 минут и более после каждого кормления / Small amounts of regurgitation for 30 minutes or more after each feeding
5	Срыгивания более половины полного объема одного кормления, не менее чем в половине кормлений / Regurgitation of more than half of the total volume of one feeding, at least in half of the feedings

DIAGNOSTICS

Criteria for establishing the diagnosis/ condition

To establish a clinical diagnosis of regurgitation/ ruminating in the newborn requires [1–4, 7, 19, 21–23, 34]:

1) careful gathering of perinatal anamnesis;
2) physical examination with assessment of physical development and detection of anxiety symptoms indicating the presence of organic pathology.

Alarm symptoms ("red flags") [2–4, 6, 7, 19]:

- appearance of regurgitation in the 1st–2nd week of life;
- lethargy, fever;
- nausea with refusal to feed;
- fountain vomiting;
- impurity of blood or bile in the vomit masses;
- aspiration of gastric contents;
- prolonged coughing, wheezing;
- stunted physical development;
- difficulty feeding or swallowing food (dysphagia, odynophagia);
- incorrect body position, namely: dystonic position of the neck — Sandifer syndrome (a rare disorder characterized by episodes of paroxysmal torticollis, sometimes with spastic nodding movements of the head, occurring against the background of the course of GERD); this syndrome is a combination of GERD with spastic torticollis and dystonic body movements, in the presence of esophageal hernia or without it;
- excessive irritability/pain;
- bulging fontanelle;
- rapid rate of increase in head circumference;
- seizures;
- weight loss;
- dysuria;
- defecation disorders (diarrhea/constipation);
- disorders up to apnea and sudden death syndrome.

Comment. *When collecting anamnesis, much attention is paid to:*

1) *peculiarities of the course of pregnancy (toxicosis, gestosis, threat of termination, edema of pregnant women, anemia, preeclampsia, exacerbation of chronic pathology, etc.) and childbirth (rapid, weakness of labor, surgical delivery, etc.), which can cause fetal hypoxia and contribute to increased regurgitation in the infant;*
2) *careful collection of genealogical anamnesis, as many diseases are hereditary in nature (e.g., pylorostenosis in 15% of cases is a hereditary pathology); there is also a genetic predisposition to the occurrence of hernia of the esophageal opening of the diaphragm [36];*
3) *the time of the first regurgitation;*
4) *the regimen, method, duration and volume of each feeding; the type of formula used in artificial feeding, the nature of maternal nutrition;*
5) *the nature of regurgitation (e.g., nocturnal, immediately after eating, time after eating, composition of regurgitant masses: curdled or uncurdled);*
6) *family history, possible environmental triggers (including family psychosocial status and factors such as parental tobacco use);*
7) *the use of pharmacologic and dietary interventions in both the infant and the mother [4].*

Although regurgitation/ruminating in newborns is often benign, some infants who present with symptoms of anxiety need further evaluation.

A more difficult subgroup of patients are considered to be infants who are fussy, cry and wriggle, have persistent regurgitation, but otherwise feel well. In this subgroup of children, families often put intense pressure on the physician to initiate antireflux therapy or diagnostic testing because of the perceived severity of symptoms [4].

In the absence of warning signs, diagnostic tests and/or treatments, including acid suppression, are NOT required unless symptoms affect feeding, growth, or achievement of key developmental stages [4, 35].

The main symptom of RS is recurrent regurgitation of recently ingested food without effort. Apart from the main sign, there is no clear consensus among diagnostic guidelines on the signs of RS, mainly due to the lack of research to support diagnostic recommendations. Due to the lack of awareness of RS, this condition is often inaccurately diagnosed or missed [37–39].

Considering the Rome Criteria, a diagnosis of RS requires the presence of symptoms **for at least two months**. These symptoms include [3, 21]:

- repetitive contractions of the abdominal muscles, diaphragm and tongue;
- mild regurgitation of gastric contents, which are either ejected from the mouth or repeatedly chewed and swallowed again;
- age of manifestation between the 3rd and 8th month;
- infants do not respond to treatment for GERD and regurgitation;
- rumination does not occur during sleep or when the infant interacts with people in the environment [40].

Complaints and anamnesis

In the presence of regurgitation/rumination in the newborn, it is **recommended** to:

- review the mother's history to identify risk factors;
- review the birth history and early neonatal period of the newborn;
- note the time of onset and progression of clinical symptoms [1–4, 7, 19–24, 34].

The level of convincingness of the recommendations is C (level of evidence — 4).

Comments. *See "Etiology and pathogenesis of the disease".*

When studying the history of a newborn with regurgitation/ruminations, it should be remembered that the main risk factors are premature birth, severe asphyxia, stressful situation in the family, dysbiosis, iatrogenic interventions leading to disruption of microbiocenosis [7, 19–24].

Physical examination

- A newborn infant with regurgitation/ruminations is **recommended** to undergo visual therapeutic examination to identify symptoms of anxiety, anthropometry with assessment of mass-height parameters [1-4, 7, 19-23, 34].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *Due to the absence of pathognomonic symptoms, first of all, it is necessary to pay attention to the presence of symptoms of anxiety, in the detection of which it is necessary to exclude organic pathology (infections, congenital malformations, metabolic disorders, GERD, etc.) [2–4, 7, 19, 21, 34, 36].*

Laboratory diagnostic tests

- It is **recommended** that newborn infants with regurgitation/ruminations in the presence of anxiety symptoms should undergo a general blood test in order to exclude/confirm infectious-toxic inflammatory process and disorders in the hemostasis system of both prenatal and postnatal genesis [41, 42].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *In case of changes in blood parameters, in-depth examination is recommended in accordance with the main causes of the development of the above-mentioned conditions (diseases).*

- It is **recommended** for newborns with regurgitation/rumination in the presence of anxiety symptoms, with poor weight gain/loss in order to identify metabolic changes arising against the background of metabolic disorders in hereditary metabolic diseases (HMDs) and severe infectious process to conduct a study of acid-base status (ABS) and blood gas composition, determination of lactic acid and ammonia levels in the blood for further diagnostic search [41, 42].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *In case of changes in the above parameters, in-depth examination is recommended.*

Instrumental diagnostic

- **Recommended** for newborns with regurgitation/rumination in the presence of heavy, persistent belches to diagnose conditions such as pyloric stenosis, hydronephrosis, ureteral obstruction, gallstones, and ovarian torsion, sliding hernia of the esophageal aperture of the diaphragm, as well as determining the length and position of the lower esophageal sphincter relative to the diaphragm, the value of the gastroesophageal angle of Gis, ultrasound examination of the abdominal cavity

(complex examination), kidneys and adrenal glands [4].

The level of convincingness of the recommendations is C (level of evidence — 5).

- It is **recommended** for newborns with regurgitation/rumination in the presence of persistent, profuse regurgitation, debuting in the first week of life, unresponsive to conventional therapies to exclude malformations (sliding hernia of the esophageal aperture of the diaphragm, malrotation, pyloric stenosis, duodenal stenosis, antral membrane, esophageal narrowing, Shatsky's rings, achalasia, esophageal strictures, and external esophageal lesions) to perform esophageal fluoroscopy with contrast [4, 34].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *Barium examination of the esophagus and stomach is performed in the straight and lateral projections and in Trendelenburg position with slight compression of the abdominal cavity. The study evaluates the permeability of the suspension, esophageal diameter, contours, wall elasticity, pathologic constrictions, ampullary dilatations, peristalsis, relief of the mucosa. To the disadvantages of the method should be attributed the fact that radiography does not always allow you to fix hernias of small size, and also gives a high radiation load.*

- It is **recommended** that newborn infants with regurgitation/rumination in the presence of anxiety symptoms should undergo videofluoroscopic swallowing studies (VFSS) in order to detect oropharyngeal dysphagia followed by aspiration, the symptoms imitating GERD [43–46].

The level of convincingness of the recommendations is C (level of evidence — 4).

Comments. *Videofluorogaphy depends on the technical capabilities of the medical organization.*

- If congenital anomalies of GI development or GI diseases of inflammatory genesis are suspected, it is **recommended** to perform esophagogastroduodenoscopy (EGDS) in newborn infants with regurgitation/rumination in order to determine the degree of mucosal lesions (ML) of the esophagus, stomach, to identify complications and to perform differential diagnosis [4].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *The study evaluates the condition of the esophageal mucosa, which is especially important in the presence of alarming symptoms (hematomesis, dysphagia, delayed weight gain). The study allows you to diagnose a number of congenital anomalies of esophageal development, acquired diseases of inflammatory and non-inflammatory nature. EGDS under general anesthesia can be considered as a safe procedure in pediatric patients [4].*

- It is **recommended** to perform a manometric study — high-resolution manometry (HRM) with or without impedance — to assess the activity of intraluminal pressure in infants with regurgitation/rumination, if there is no effect on the current therapy in case of suspected congenital neuromuscular diseases or esophageal malformations [4, 30, 34, 47–51].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *High-resolution manometry is now being performed to assess esophageal motility, providing a more detailed view of intraluminal pressure activity than conventional manometry. Based on pediatric studies, HRM may be of value for evaluating "R teeth" and retrograde bolus flow to diagnose rumination that mimics intractable reflux symptoms [30, 34, 47–51]. Manometric study depends on the technical capabilities of the medical organization.*

Other diagnostic tests

Diagnosis of diseases associated with regurgitation, vomiting is performed on indication [52].

TREATMENT

Therapeutic measures in the presence of regurgitation in newborns include a complex of non-medicamentous effects, mainly normalization of lifestyle, daily regimen, nutrition and conservative therapy. The choice of treatment method or their combination is made depending on the cause, severity and possible complications [4, 52].

Conservative treatment

Postural therapy

- It is **recommended** that newborns with regurgitation use postural therapy, i.e. treatment by changing the position of the body: when feeding, hold the baby at an angle of 45–60°, which prevents regurgitation and aerophagia. At night, it is advisable to raise the head end of the crib by 10–15 cm [4, 6, 7, 19].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *Keep the baby in an upright position after feeding should be kept for at least 20–30 minutes (with the head elevated). Giving the newborn a forced position during sleep (raised head end of the bed, especially horizontal position on the stomach) is not recommended due to the high risk of sudden infant death syndrome.*

Diet therapy

- In newborn infants with regurgitation, dietary adjustments are **recommended** [4, 6, 7, 19, 52].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *In natural feeding, it is recommended to create a calm environment for the nursing mother aimed at preserving lactation, normalize the child's feeding regimen, avoiding overfeeding and controlling correct breastfeeding to prevent aerophagia.*

- It is **recommended** to increase the frequency of feedings with a decrease in the single volume of formula [6, 7, 19].

The level of convincingness of the recommendations is C (level of evidence — 5).

- In the absence of evidence of intolerance to cow's milk proteins, it is **recommended** to transfer the child to one of the specialized foods — antireflux (AR) milk formula, the viscosity of which is increased by introducing one of the thickeners into its composition [4, 6, 7, 19].

The level of convincingness of the recommendations is C (level of evidence — 5).

Comments. *Two types of polysaccharides are used as thickeners — non-digestible (carob bean gluten — gum) and digestible (modified starches). The gum or starch (rice, corn or potato) in AR formulas binds liquid and swells when it enters the baby's stomach, making the mixture thicker and preventing backflow into the esophagus and mouth. AR products are introduced into the child's diet gradually, at each feeding. The volume of the therapeutic formula is selected individually until regurgitation stops. The effect from the use of AR-formula enriched with starch comes in a more distant period compared to AR-formula containing gum. AR products are recommended for children with both normal stools and a tendency to unstable stools [53, 54]. Starch-containing formulas are recommended to be prescribed in full daily volume. Despite the high clinical efficacy of AR products, they should not be used uncontrolled as an alternative to conventional standard milk formula (SMF). AR-formulas are used at a certain stage of regurgitation syndrome treatment, as indicated. The duration of their use is individualized, sometimes it is quite long (up to 2–3 months), and only after achieving a persistent therapeutic effect the child is transferred to SMF [3, 6, 7, 19, 53, 54].*

- The use of deep protein hydrolysis (DPH) or amino acid-based formulas, which can reduce regurgitation episodes in children with cows milk protein intolerance, has been **recommended** if dietary correction with AP formulas is ineffective for 2–4 weeks [6, 7, 19].

The level of convincingness of the recommendations is B (level of evidence — 2).

Comments. *Formulas based on DPH are indicated when the child has other symptoms indicative of atopic (allergic) diseases [4, 6, 7, 19]. Lack of improvement of the clinical picture within 2–4 weeks indicates the ineffectiveness of the chosen tactics of diet therapy. In case of a positive effect, it is recommended to continue taking the formula for up to 12 months, but not less than 6 months [43, 55].*

Drug therapy

- The use of drugs such as proton pump inhibitors (PPI) (ATX code A02BC)(#esomeprazole**) is **not recommended** in infants with regurgitation/rumination due to lack of scientific evidence and potential risk of adverse events [4, 55–61].

The level of convincingness of the recommendations is B (level of evidence – 2).

Comment. *PPI (ATX code A02BC) in children at different doses may have little or no symptomatic or endoscopic effect. There is no statistical superiority of one PPI (ATX code A02BC) over another [59].*

- Acid-suppressive therapy with PPI antagonists (ATX A02BC code) (#esomeprazole**) has been **recommended** for infants whose condition has not improved with strict adherence to postural and nutritional therapy and/or with moderate to severe esophagitis [55, 61–64].

The level of convincingness of the recommendations is C (level of evidence – 3).

Comments. *#Ezomeprazole** (ATX code A02BC05) is administered in a daily dose of 0.5 mg/kg for 1–2 doses. The average duration of therapy is 4–6 weeks. Contraindications: individual intolerance to the drug [4]. Reduction of treatment duration is not recommended [59].*

- Administration of stimulants of GI motility (ATX code A03FA) and antacids in combination with other drugs (ATX code A02AX) is **not recommended** for infants with regurgitation/rumination [4, 59, 65].

The level of convincingness of the recommendations is C (level of evidence – 5).

Comments. *Evidence from RCS is insufficient to assess the efficacy of gastrointestinal motility stimulants (prokinetics) (ATX code A03FA) and antacids in combination with other drugs (ATX code A02AX) [4, 59, 65].*

- The routine use of antidiarrheal drugs of biological origin that regulate the balance of intestinal microflora (probiotics) (ATX code A07FA) in neonates with regurgitation/rumination is **not recommended**.

The level of convincingness of the recommendations is B (level of evidence – 3).

Comments. *The evidence from RCS is not strong enough to actively recommend antidiarrheal drugs of biological origin that regulate the balance of intestinal microflora (probiotics) (ATX code A07FA) in neonates with regurgitation.*

Surgical treatment is not applicable.

Other treatment is not applicable.

Medical rehabilitation and sanatorium-resort treatment, medical indications and contraindications to the use of medical rehabilitation methods, including those based on the use of natural therapeutic factors are not applicable.

PREVENTION AND MEDICAL FOLLOW UP, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

- It is **recommended** to prevent regurgitation/rumination in newborns by taking measures aimed at preventing etiologic factors: perinatal hypoxia, asphyxia; fighting for natural childbirth, breastfeeding; creating a favorable environment in the family, as well as friendly, attentive attitude to the newborn [7, 19, 21-25].

The level of convincingness of the recommendations is C (level of evidence – 5).

- Follow up of infants with regurgitation/rumination by a pediatrician is recomended. Pediatrician monitor physical development indicators, hold explanatory talks with parents about their child's health status and feeding rules, and give **recommendations** regarding the diet of the lactating mother [7, 12, 19].

The level of convincingness of the recommendations is C (level of evidence – 4).

ORGANIZATION OF MEDICAL CARE

For prevention, timely diagnosis and choice of further management tactics for newborns with rumination/regurgitation, medical care is provided in medical institutions of the *first* (medical institutions providing primary medical and sanitary assistance to the population with basic and specialized profiles), *second* (medical institutions providing medical assistance in certain profiles) and *third* levels, with specialized and high-tech medical care, consultations with specialists (neonatologist, neurologist, gastroenterologist, allergist-immunologist, pediatric surgeon), examination and therapy.

Indications for hospitalization in a medical organization for newborns with rumination/regurgitation [1, 7]:

- persistent regurgitation that cannot be corrected;
- presence of persistent, pronounced symptoms of anxiety (regurgitation alternating with vomiting; blood and/or bile in the refluxate), leading to significant weight loss, symptoms of dehydration, electrolyte

and metabolic disorders, as well as respiratory symptoms associated with regurgitation (laryngospasm, bronchospasm, aphonia, cough).

Indications for discharge from a medical organization of ruminating/regurgitating newborns:

- management of anxiety symptoms;
- stabilization of the condition;
- exclusion of organic nature (surgical, infectious, endocrine, metabolic, allergic, neurological, etc.).

After discharge from the hospital, children are subject to outpatient observation by a pediatrician and other specialists depending on the identified etiology (neurologist, gastroenterologist, endocrinologist, surgeon, geneticist, etc.).

The decision on the need for re-hospitalization is made by the pediatrician or specialist on a case-by-case basis.

Issues related to the rehabilitation of infants with regurgitation/rumination are decided by a pediatrician on an individual basis.

ADDITIONAL INFORMATION (INCLUDING FACTORS AFFECTING THE OUTCOME OF THE DISEASE OR CONDITION)

The prognosis for regurgitation/ruminations is predominantly favorable. However, frequent regurgitation in infancy may have long-term health consequences, increasing the risk of heartburn, vomiting and acid belching [66].

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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90TH ANNIVERSARY OF THE DEPARTMENT OF PROPAEDEUTICS OF CHILDREN'S DISEASES OF THE LENINGRAD, SAINT PETERSBURG PEDIATRIC MEDICAL INSTITUTE, ACADEMY, UNIVERSITY

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ABSTRACT. The article describes the 90-year history of the creation and development of the Department of Propaedeutics of Childhood Diseases with a course of general care for children at St. Petersburg State Pediatric Medical University. Historical aspects of the development of propaedeutics of childhood diseases through the activities of the heads of the department and its employees are reflected. The scientific areas of the department's activities, the contribution of its employees to the clinical activities of the St. Petersburg State Pediatric Medical University clinic and health care institutions of St. Petersburg are described. The close relationship between the department and clinical bases provides the opportunity to integrate educational, clinical, scientific and innovative activities as a single pediatric school, which is so necessary for the development of domestic healthcare.

KEYWORDS: *Department of Propaedeutics of Childhood Diseases with a course of general child care at Saint Petersburg State Pediatric Medical University, anniversary, M.S. Maslov, A.F. Tur, I.M. Vorontsov, A.B. Volovik. V.V. Yuryev, E.M. Bulatova, pediatric school*

90 ЛЕТ КАФЕДРЕ ПРОПЕДЕВТИКИ ДЕТСКИХ БОЛЕЗНЕЙ ЛЕНИНГРАДСКОГО, САНКТ-ПЕТЕРБУРГСКОГО ПЕДИАТРИЧЕСКОГО МЕДИЦИНСКОГО ИНСТИТУТА, АКАДЕМИИ, УНИВЕРСИТЕТА

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РЕЗЮМЕ. В статье изложена 90-летняя история создания и развития кафедры пропедевтики детских болезней с курсом общего ухода за детьми СПбГПМУ. Отражены исторические аспекты становления пропедевтики детских болезней через деятельность заведующих кафедры и ее сотрудников. Описаны научные направления деятельности кафедры, вклад ее сотрудников в клиническую деятельность клиники СПбГПМУ и учреждений здравоохранения Санкт-Петербурга. Тесная взаимосвязь кафедры и клинических баз обеспечивает возможность интеграции образовательной, клинической, научной и инновационной деятельности как единой педиатрической школы, столь необходимой для развития отечественного здравоохранения.

КЛЮЧЕВЫЕ СЛОВА: *кафедра пропедевтики детских болезней с курсом общего ухода за детьми СПбГПМУ, юбилей, М.С. Маслов, А.Ф. Тур, И.М. Воронцов, А.Б. Воловик, В.В. Юрьев, Е.М. Булатова, педиатрическая школа*

Formally, the Department of Propaedeutics of Childhood Diseases dates back to September 1934, that is, in 2024 it celebrated its 90th anniversary. The history of the Department of Propaedeutics of Childhood Diseases with the course of general child care is the history of St. Petersburg and national pediatrics.

At the same time, the staff of the future department was formed back in 1928 within the Institute of Maternity and Infancy, where the Laboratory of Childhood Physiology was organized, which was headed by Mikhail Stepanovich Maslov for two years (Fig. 1). For more than 40 years of clinical, scientific and pedagogical activity, M.S. Maslov managed to create his own pediatric school of like-minded people. M.S. Maslov personally trained 10 doctors and 46 candidates of medical sciences. M.S. Maslov is the author of more than 200 scientific works, including 16 monographs, 8 textbooks, several manuals. Studying the peculiarities of childhood, M.S. Maslov evaluated them from the point of view of morphofunctional differentiation of organs and systems of the growing organism, and any pathological conditions — from the position of their possible negative impact on the process of this differentiation. This defined the concept of "Maslov's school".

After M.S. Maslov, the department was headed by Alexander Fedorovich Tur, a pupil of N.P. Gundobin and M.S. Maslov, a professor of the Military Medical Academy. After the organization on the basis of the Institute of Maternity and Infancy, for many years the only one in the world, the entire staff of the laboratory moved to the Department of Propaedeutics of Childhood Diseases. At first the staff of the department was small — only 5 teachers. The physiologic department with 50 beds became the base of the department. The staff of the department faced an extremely difficult task of organizing the educational process, determining the

Fig. 1. Heads of the Department from 1934 to 2019. Top row: M.S. Maslov, A.F. Tur, A.B. Volovik. Bottom row: I.V. Vorontsov, V.V. Yuryev, M.M. Khomich, V.I. Purin, E.M. Bulatova

Рис. 1. Заведующие кафедрой с 1934 по 2019 гг. Верхний ряд: М.С. Маслов, А.Ф. Тур, А.Б. Воловик. Нижний ряд: И.М. Воронцов, В.В. Юрьев, М.М. Хомич, В.И. Пуринь, Е.М. Булатова

goals and objectives of the new discipline, with which the staff of the department coped brilliantly, and the basic principles of teaching formulated at that time have been preserved to the present time.

At the same time, scientific research continued intensively at the department. The main issues of nutrition, rehabilitation and child upbringing were developed, which were later used in the organization of orphanages in our country. A.F. Tur is the author of more than 250 published scientific works, including 7 monographs, reference books, 3 textbooks and 4 manuals. The most important monographs were published in the pre-war period: "Practical Hematology of Childhood" (1931), "Handbook on Dietetics of Early Childhood" (1935), "Physiology and Pathology of the Newborn Period" (1936), "Gymnastics of the Early Childhood" (1937), "Propaedeutics of Childhood" (1940). It was hematology, neonatology, age physiology and dietetics that became the main problems of A.F. Tur's department for many years. A.F. Tur trained 28 doctors and 110 candidates of medical sciences, he is rightly considered the creator of the largest pediatric school. His students were Professors A.M. Abezgauz, I.M. Vorontsov, R.F. Ezersky, V.I. Kalinicheva, Y.R. Kovalev, M.N. Nebytova-Lukyanchikova, A.V. Papayan, L.M. Skorodok, G.M. Slutskaya, N.P. Shabalov, L.V. Erman, Associate Professor O.F. Tarasov and others.

Since 1939, the Department of Propaedeutics of Childhood Diseases was headed for 31 years by Arkady Borisovich Volovik, a student of N.I. Krasnogorsky (Fig. 1). With his arrival and actually new staff, the scientific direction of the department changed fundamentally. The main directions of research were heart diseases, and first of all rheumatism, the prevalence of which in those years was extremely high. This direction of scientific research for many years became one of the main directions of research work of the department as very promising and nowadays. Arkady Borisovich has more than 180 scientific works, including such monographs as "Recognition and Treatment of Rheumatism in Children" (1939), "Heart Diseases in Children" (1948), "Rheumatism in Children" (1948), which have become table books for many generations of pediatricians and cardioreumatologists.

With the active participation of Arkady Borisovich in the mid-1950s, a rheumatology service was organized in Leningrad, which implied a stage: "hospitalization — rehabilitation in a local sanatorium — polyclinic stage of observation" with a clearly defined multiplicity, which by that time was one of the perfect specialized services in children's health care in our country. During the war years, the entire staff of the department, headed by Arkady Volovik, remained in besieged Leningrad. They did not stop their pedagogical and therapeutic activities for a single day. Thousands of little patients of besieged Leningrad owe their lives to the staff of the Department of Propaedeutics of Childhood Diseases. It is curious that even in these years continued scientific work related to the nutrition of children in conditions of food shortage and treatment of dystrophy.

Under the guidance of A.B. Volovik, 9 doctoral and 47 candidate dissertations were performed and a school of Russian cardio-rheumatologists was actually created. Among A.B. Volovik's pupils are S.A. Gavrilov, D.M. Shilevskaya, J.J. Rappoport, V.V. Yuriev, A.Y. Trubina, V.I. Reznik.

In 1970, Igor Mikhailovich Vorontsov, a student of A.F. Tur, was elected head of the department (Fig. 1). During these years V.V. Yuryev, V.I. Reznik, N.V. Ananyina, V.I. Purin, A.Y. Puchkova, A.D. Ziselson, and R.V. Boldyrev worked in the department. Somewhat later A.V. Kharchev, N.M. Letenkova, D.S. Korostovtsev, A.S. Simakhodskii, N.I. Vitina and many others joined the department.

Continuing the traditions of the department, the main direction of scientific research at that time was the clinical and immunologic study of rheumatic diseases in children. Under the leadership of I.M. Vorontsov, immunosuppressive therapy of systemic lupus erythematosus and severe, disabling forms of rheumatoid arthritis in children began to be used at the department for the first time in the country with great success since 1967. Due to these therapeutic technologies it was possible to sharply reduce the frequency of disability of these patients and minimize the loss of vision in patients with rheumatic uveitis. On the initiative of I.M. Vorontsov, studies on the clinic and immunopathogenesis of allergic diseases in children were initiated at the Institute and at the Department. The most important works in this direction were those that showed the equal importance of both immunologic intolerance and vegetative imbalance in the genesis of atopy and atopic diseases. The doctrine of age-specific transient atopy of young children was formulated. The regularities of food allergy evolution were developed.

For many years, the department successfully developed the medical basis for the use of various automa-

ted technologies in pediatrics. For the creation of the automated system of preventive examinations the staff of the department and engineers were awarded the prize of the Council of Ministers of the USSR in 1991 year.

I.M. Vorontsov trained about 90 candidates of medical sciences, 20 doctors of medical sciences. Among his students are G.A. Novik, N.V. Slizovsky, E.V. Baryshek, K.S. Bystrova, I.V. Makarova, G.A. Kopytov, A.F. Bogatyrev, I.A. Kelmanson, A.V. Adrianov, and others.

During the time he was the head of the Department of Propaedeutics of Childhood Diseases, he published more than 200 scientific works, including such monographs as “Leukemia in Children”, “Handbook of Childhood Dietetics”, “Food Allergy in Children”, together with Professor A.V. Mazurin he published “Textbook on Propaedeutics of Childhood Diseases”, which can be considered a guide to this discipline by the careful selection of materials, their volume. In general, I.M. Vorontsov is the author of 14 monographs, 2 textbooks and more than 250 works in scientific medical journals, 17 certificates of authorship and 2 patents for inventions.

In connection with the reorganization of the departments of Pediatrics of the Institute in 1986, Igor M. Vorontsov became the head of the Department of Pediatrics No. 3. A student of Arkady Borisovich Volovik and Igor M. Vorontsov, Professor, Doctor of Medical Sciences Vladimir V. Yuryev, was elected as the head of the Department of Propaedeutics of Childhood Diseases (Fig. 1). The staff of the new department consisted of both members of I.M. Vorontsov's department and new employees. In the following years, the department was staffed by G.I. Berlin, N.A. Batanova, G.V. Krasin'kova, M.M. Homich, T.M. Vlasova, O.V. Dumanovskaya, E.I. Aleshina, V.D. Nazarov, B.N. Savchenko, A.S. Simahodskij, V.P. Andrezen, N.N. Voronovich, A.YA. Puchkova, V.I. Purin', E.I. Zhestyannikova, G.A. Tarusinov, M.V. Erman, N.V. Paharenko, I.A. Leonova, E.A. Usychenko, E.YU. Gurkina, S.V. Bairova, E.G. Hramcova, O.YU. Bolueva, O.N. Majorova, A.V. Ivanov, T.M. Pervunina, M.SH. CHezhiya, V.B. Artemova, N.R. Balakleec, I.YA. Il'ina, V.P. Novikova, E.V. Bojcova, S.A. Zorina, O.A. Minochkina, O.M. Cekh, L.D. Fedorich, I.V. Romanova, L.L. Gorbacheva et al.

The main criterion for selecting staff to work at the department was the presence of professionalism and personal human qualities (decency, kindness, responsiveness, love for children, ability to live and work in a team sometimes in very difficult situations).

One of the first tasks that faced the new head of the department, was the reorganization of teaching according to the principles proposed by A.F. Tur and, in connection with the arrival of new staff at the department, the unification of teaching and providing staff with methodological material. For each lesson, sets of methodical materials were created, which included annotations of the lesson itself, abstracts of the lecture material, initial and final level tests. The methods and techniques of direct examination of the child were collegially discussed, refined and approved at departmental meetings, which allowed to develop a unified approach to teaching and assessment of students' knowledge. Numerous educational and methodical manuals were published to help students and doctors, for example, “Evaluation of the main anthropometric indices of the North-West”, etc. The department's staff published a monograph of the Department of Pediatrics. All the main sections of Propaedeutics of Childhood Diseases “Growth and Development of a Child”, “Care for a Healthy and Sick Child”, “Direct Examination of Children”, “Nutrition of Early Childhood” have been published as monographs by the staff of the department; in 2012 the “Textbook of Propaedeutics of Childhood Diseases” was published. Invaluable assistance in methodical work to V.V. Yuriev was provided by A.Ya. Puchkova, who worked as the head of the teaching part of the department for more than 25 years, provided invaluable assistance to Prof. V.V. Yuriev in methodical work (Fig. 1). For more than 50 years of labor activity Alla Yakovlevna educated more than one generation of pediatricians and, having a scientific degree of candidate of medical sciences, for her outstanding achievements by special order of the rector Vladimir Viktorovich Levanovich, was appointed to the position of professor.

In the 1990s, the department organized a course of pediatric diseases for the Faculty of Medicine, which was headed by Professor V.I. Purin. The members of the department performed great social work. All the years of chairing the department V.V. Yuriev was the chief cardio-rheumatologist of the Leningrad region. He also headed the commission for 10 years to assess the condition of children for adoption. Professor V.I. Purin was the chief pediatrician of the Leningrad region for more than 20 years, Professor A.S. Simakhodsky was the head of the department of maternal and child protection of the Health Committee of our city; the chief

specialist in child nutrition of the Health Committee of the Government of St. Petersburg was Associate Professor E.I. Aleshina, and the chief pediatric nephrologist of the Health Committee of the Leningrad region was Professor M.V. Erman.

The staff of the department developed an original system of automated examination of the child population Sanus and a set of examinations to decide on the influence of various factors on the child's health. Studies were conducted in Leningrad (St. Petersburg), Leningrad, Novgorod regions, the Komi Republic, Karelia, and Yakutia. The staff of the department actively participated in the evaluation of the health of children in Belarus who suffered as a result of the Chernobyl catastrophe. For 20 years more than 50 thousand children were subjected to complex examination. The results of these studies were published in numerous articles and dissertations.

During his tenure at the department Vladimir Vladimirovich Yuriev published more than 200 scientific papers, prepared 36 dissertations, including 6 doctoral theses. Among the pupils of V.V. Yuriev — Professor V.I. Purin, Professor A.S. Simakhodsky, Professor M.V. Erman, Professor M.M. Khomich, Professor V.P. Novikova, Professor M.P. Korolev, Professor V.I. Makarova, Associate Professor E.I. Aleshina, Candidate of Medical Sciences O.Y. Parshutkina, Candidate of Medical Sciences S.V. Bairova and many others.

Since 1990 the direction of scientific researches of the department was the problems of pediatric nephrology. It was headed by Prof. M.V. Erman. Various aspects of diagnostics of nephropathies, malformations of kidneys and urinary tract, small kidney, therapy of cystitis were analyzed.

Since 2006, in connection with the arrival of V.P. Novikova at the department began research on pediatric gastroenterology. Together with immunologists, pathomorphologists, geneticists and infectious diseases specialists fundamental studies were conducted, age specific features of chronic gastroduodenal pathology were studied, new methods of diagnostics and treatment of diseases of digestive organs in children were developed. Valeria Pavlovna's merit in that period was the preparation and reading of the whole cycle of lectures and practical classes on pediatrics for English-speaking students of the Faculty of Medicine.

In 2008, the department was headed by Dr. Mikhail Mikhailovich Khomich, a graduate of the Department of Propaedeutics. Mikhail Mikhailovich passed the way from clinical resident to the head of the department (Fig. 1). He was always distinguished by enthusiasm, diligence, genuine interest in clinical problems of pediatrics and the formation of children's health. It was at this time that the department developed and introduced into the educational process workbooks, lecture notebooks for the medical faculty in Russian and English, filmed and edited educational films. Thanks to M.M. Khomich, computer technologies were actively introduced into the work of the department, the work of the Student Scientific Society Circle (SSC) was intensified, a competition for the best in the specialty was organized. The sudden tragic death of Mikhail Mikhailovich shook all the staff of the department and became a great loss for all those who knew him.

In 2009 the department was headed by Professor V.I. Purin — a talented scientist, clinician, rheumatologist, veteran of the department, who came to the department as an experienced doctor. Vladimir Ivanovich was distinguished by a high erudition, organizational talent, demanding to himself and the staff. Professor's rounds were a model of the highest professionalism, they were conducted in full compliance with the best traditions of St. Petersburg school of pediatricians. Vladimir Ivanovich's lectures to the students of the Faculty of Medicine were read at such a high level that they were interesting for practicing physicians as well. V.I. Purin is the author of numerous scientific works published in the leading Russian journals. Dr. Evgenia V. Boitsova, MD, professor, a pulmonologist, a well-known specialist in chronic bronchopulmonary pathology in children in Russia and abroad, the cheif pediatric pulmonologist of the Leningrad Region, taught at the Faculty of Medicine.

For many years the department was a big family, uniting professionals of the highest level: nephrologists, gastroenterologists, pediatricians, endocrinologists, cardiologists, pulmonologists, functional diagnosticians. Traditions of the department were passed on to the youth, starting from the student bench, by professor's admonitions, author's methods of associate professors, daily, painstaking labor of assistants. The team was very friendly, the employees were united by common interests and mutual assistance. Warm human relations, family friendship contributed to joint leisure activities, trips to the countryside, participation in amateur activities.

In 2010, by order of the Rector V.V. Levanovich, the head of the department was appointed Elena Markovna Bulatova (Fig. 1) — vice-president of the St. Petersburg branch of the Union of Pediatricians of Russia, chief specialist in child nutrition of the Health Committee of the Government of St. Petersburg. Elena Markovna is actively engaged in public activities — she is a member of the Council on Health Care and Demographic Policy under the Plenipotentiary Representative of the President of the Russian Federation in the North-West Federal District, a member of the Problem Commission on Child Nutrition and the profile commission of the Expert Council on Dietetics of the Ministry of Health of the Russian Federation, a member of the Expert Council of the "National Program to Optimize the Feeding of Children of the First Year of Life", the Expert Coordination Council for the Development of Healthy and Social Nutrition. Elena Markovna is a member of the organizing committees of leading Russian congresses.

With the arrival of E.M. Bulatova, the staff of the department changed. Most of the staff, who had worked at the department for many years, moved to the V.A. Almazov Scientific Medical Research Center, where the Department of Pediatrics was organized, and to the First State Medical University named after I.P. Pavlov. I.P. Pavlov First State Medical University, where the Department of Pediatrics was organized. For work at the department were invited Dr. M.D., Professor T.V. Kosenkova, Dr. M.D., Professor R.B. Tsallagova, Dr. M.D., Professor Z.V. Nesterenko, Ph, Associate Professor O.A. Mataligina, Candidate of Medical Sciences, Associate Professor N.M. Bogdanova, Candidate of Medical Sciences, Associate Professor M.D. Shestakova, Candidate of Medical Sciences, Associate Professor M.S. Trukhmanov, Candidate of Medical Sciences, Associate Professor A.L. Balashov, Candidate of Medical Sciences S.A. Teplyakova, Candidate of Medical Sciences O.V. Lagno, A.P. Gerasimov, A.M. Konstantinov, I.S. Volkova, O.V. Guzeyeva, V.A. Gurieva, A.A. Efimova, E.V. Boytsova, A.A. Seliverstova and other staff members who had to master the teaching of propaedeutics of pediatric diseases themselves. The leading problems of scientific and practical activity of E.M. Bulatova were the issues of pediatric nutrition. E.M. Bulatova is the author of 145 scientific papers, 2 PhD theses were defended under her supervision. In 2013, the Committee for Science and Higher Education of the Government of St. Petersburg awarded the title "Leading Scientific and Pedagogical School under the guidance of Professor E.M. Bulatova" to the team led by Elena Markovna. However, from 2010 to 2020 no dissertations were defended at the department. The staff was constantly renewed.

In 2020, V.P. Novikova, Doctor of Medical Sciences, Professor, returned to the department and headed it. Under the leadership of Valeria Pavlovna 13 candidate and 2 doctoral dissertations were defended. Among her students are Professor M.M. Gurova, Professor A.N. Zavyalova, Associate Professor A.M. Shabalov, Associate Professor A.N. Petrovsky, Associate Professor A.O. Sidorkin, N.S. Shapovalova, A.P. Listopadova, M.Y. Komissarova, O.M. Tsekh and others. Valeria Pavlovna Novikova, a student of V.V. Yuriev, is the author of more than 950 scientific works, including co-author of 5 textbooks, 5 national manuals, 4 manuals for doctors, 18 monographs, 13 patents of the Russian Federation. Today, the department headed by V.P. Novikova has the following employees Doctor of medical sciences, Professor E.V. Boytsova, Doctor of medical sciences, Professor M.M. Gurova, Doctor of medical sciences A.N. Zavyalova, Doctor of medical sciences T.N. Doronina, Candidate of Medical Sciences N.V. Evdokimova, Candidate of Medical Sciences N.M. Bogdanova, Candidate of Medical Sciences M.S. Trukhmanov, Candidate of Medical Sciences A.L. Balashov, Candidate of Medical Sciences A.P. Listopadova, Candidate of Medical Sciences A.Y. Trapeznikova and promising talented young people.

The main task of the department is to return to the traditions of the V.V. Yuriev school. The department has updated methodological manuals for students, created new films on inspection techniques and presentations for all classes. All this proved to be in great demand during the period of pandemic and remote learning. Methodological manuals for graduate accreditation and workshops have been created, which are in demand in other universities in Russia. Teachers regularly discuss methodological issues, including at interdepartmental meetings. Currently, the department trains not only future pediatricians, but also students of medical, medical-preventive, dental faculties, faculties of nursing and medical biophysics. There are two student scientific clubs at the department, one of them is in English. In 2023 the scientific club of the Department of Propaedeutics of Pediatric Diseases received the Diploma of

the best section. Every year up to 10–15 scientific papers of students with teachers of the department are published. Together with students for 3 years registered 4 patents, 3 databases. In 2022–2023 academic year students presented 4 reports at conferences abroad. Under the guidance of V.P. Novikova, the department conducts activities to implement the programs “Healthy Lifestyle”, “Patriotic Education”, “Formation and formation of student personality”, “Spiritual and moral formation” within the framework of the educational work program of Federal Stste Budgetary Educational Institution of Higher Education SPbSPMU of the Ministry of Health of the Russian Federation.

Training in clinical residency and postgraduate studies is carried out. For the first time 4 author's cycles of Continuous Medical Education at the Faculty of Postgraduate Education in Pediatrics and Gastroenterology and Dietetics were created and are held. Monthly meetings of the discussion club for doctors “Early Childhood. Problems and Solutions" are organized monthly. Once every two years the All-Russian conference “Knowledge of propaedeutics — the basis of clinical thinking of a pediatrician” is held. In the jubilee year 2024, the third conference on propaedeutics was held, where representatives of all departments teaching students propaedeutics of childhood diseases in the Russian Federation shared their teaching experience, discussed the methodology of evaluation of practical skills, and participated in several master classes. Conference with international participation “Food intolerance” is held annually. Employees of the department are heads — administrative staff of medical organizations: Professor M.M. Gurova is the deputy chief physician for medical department of St. Petersburg State Budgetary Institution “Consultative and Diagnostic Center for Children”; Associate Professor A.L. Balashov is the chief physician of St. Petersburg State Budgetary Institution “City Polyclinic No. 56”. Also the staff of the department actively participate in the life of the University: A.N. Zavyalova consults patients of the clinic of SPbSMU as a nutritionist, and also conducts appointments once a week in the Consultative and Diagnostic Center of SPbSMU; assistant A.V. Gogolev regularly conducts appointments in the Consultative and Diagnostic Center of SPbSMU; assistant N.V. Evdokimova consults patients of the endocrine department of the clinic of SPbSMU as a nutritionist. In 2020-2021, Associate Professor of the Department N.M. Bogdanova went on business trips to Kaliningrad, Salekhard, Vologda, Cherepovets, Podporozhye (Leningrad region) to provide medical care to the pediatric population. In 2021, the assistant of the department N.V. Evdokimova went on a business trip as part of a team to the Chechen Republic to conduct medical examination of the child population. In 2022, Associate Professor A.Y. Trapeznikova and Associate Professor N.M. Bogdanova traveled to the Republic of Karelia (Petrozavodsk) as part of a team of physicians and residents of St. Petersburg State Pediatric Medical University to assist local health care institutions during the pandemic of a new coronavirus infection. In 2023 the assistant A.V. Gogolev went on a business trip to the Luhansk People's Republic as a part of the working group to conduct medical examination of children of Lutuginsky special (correctional) boarding school. In 2023, the assistant of the department N.V. Evdokimova, being an expert of the SPbSPMU on outpatient care, traveled on business trips to assess the quality of medical care for children in the regions of the North-West Federal District. The Department of Propaedeutics of Childhood Diseases with the course of general child care conducts joint activities with social protection institutions: St. Petersburg State Social Security Institution “Boarding Home for Children with Mental Developmental Disabilities No. 4” and St. Petersburg State Clinical Hospital “Hospice No. 1” of St. Petersburg.

The department deals with the problems of pediatric gastroenterology, functional diseases and chronic pathology of the upper digestive tract. Criteria for diagnosing autoimmune gastritis in children have been developed, the peculiarities of GI lesions in comorbid pathology have been studied. Nutritional status of children with different pathologies is actively studied. A "decision tree" for the choice of nutritional support methods in nutritional status disorders has been developed. Genetic and epigenetic factors of obesity development in children are described. The concept of sarcopenia in children was developed and methods of its diagnostics were patented. The staff of the department of propaedeutics of pediatric diseases with the course of general care of children have scientific publications in journals, reviewed by VAK systems (in 2022 the staff had 38 publications, in 2023 the staff had 56 publications), Scopus (in 2022 the staff had 12 publications, in 2023 the staff had 21 publications). The Hirsch index of

Fig. 2. Department staff in 2024. Bottom row: K.A. Kravtsova, A.Yu. Trapeznikova, N.V. Evdokimova, Yu.E. Zamyatina, D.M. Magamedova. Top row: L.A. Firsova, M.S. Trukhmanov, M.D. Shestakova, V.P. Novikova, A.N. Zavyalova, A.E. Blinov, N.M. Bogdanova, A.P. Listopadova

Рис. 2. Коллектив кафедры в 2024 году. Нижний ряд: К.А. Кравцова, А.Ю. Трапезникова, Н.В. Евдокимова, Ю.Е. Замятина, Д.М. Магамедова. Верхний ряд: Л.А. Фирсова, М.С. Трухманов, М.Д. Шестакова, В.П. Новикова, А.Н. Завьялова, А.Е. Блинов, Н.М. Богданова, А.П. Листопадова

the department is 9.6. The Hirsch Index of the Head of the Department, Doctor of Medical Sciences, Professor V.P. Novikova is 34.

Professor V.P. Novikova, Head of the Department, is Deputy Editor-in-Chief of the journal “Children's Medicine of the North-West” (included in the VAK list) and the journal “Medicine: Theory and Practice” (included in the VAK list), a member of the editorial board of the journal “Preventive and Clinical Medicine” (included in the VAK list, K2) and the journal “University Therapeutic Bulletin” (included in the VAK list). Professors, Drs. M.M. Gurova, E.V. Boitsova are members of the editorial board of the journal “Children's Medicine of the North-West”.

The members of the department not only actively publish scientific works, but also participate in the edition of the book “Consultant in 5 minutes” (the title editor of the book is Novikova V.P.). Valeria Pavlovna was one of the title editors of the multi-volume edition of “Pediatrics by Nelson”.

The department is in the process of forming a cohesive team: this is facilitated by joint travels, excursions, meetings, trips to the theater.

St. Petersburg school of propaedeutics has found continuation in its pupils working in different departments and in medical institutions of St. Petersburg and beyond. The knowledge gained from the teachers is passed on to the younger generation of young scientists and doctors of various profiles. Preservation and multiplication of traditions of St. Petersburg pediatric school of propaedeutics is the guarantee of prosperity of the national pediatrics!

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» (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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ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА И ИЗМЕНЕНИЯ ЕГО УСЛОВИЙ

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.

ОФОРМЛЕНИЕ РУКОПИСИ

Редакция журнала приветствует полностью двуязычные статьи.

Статья должна иметь **(НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ)**:

1. **Заглавие** (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.

2. **Сведения об авторах** (публикуются). Для каждого автора указываются: фамилия, имя и отчество, ученая степень, место работы, почтовый адрес места работы, **e-mail, ORCID, SPIN-код.** Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях или по системе BGN (Board of Geographic Names), см. сайт http://www.translit.ru.

3. **Резюме (Abstrsct)** (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Children's Medicine of the North-West» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

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.

В оригинальных статьях допускается цитирование, как правило, не более 30 источников, в обзорах литературы — не более 60, в лекциях и других материалах — до 15. Библиография должна содержать большинство публикаций за последние 5 лет.

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

Если публикация написана ***на русском языке*** (на кириллице) и существует официальный перевод на английский язык, нужно привести этот вариант. Если официального перевода нет, следует перевести название публикации на английский язык самостоятельно. В конце описания в скобках указать язык издания.

Если цитируемая статья написана ***на английском*** (немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования и в 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).

Стандарт транслитерации. При транслитерации рекомендуется использовать систему BGN (Board of Geographic Names), см. сайт http://www.translit.ru.

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 так же, как в предыдущих публикациях или по системе BGN.

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 перевести на английский язык самостоятельно.

Название издания (журнала). Некоторые неанглоязычные 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), PubMed. 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, то есть Moscow, а не «Moskva» и не «M.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. Название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Приказы, указы, постановления и другие официальные документы, а также патенты транслитерируются.

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. Vol. 3. Moscow; 2019: 203–227. (In Russian).

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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 accounts 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 at: 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 таблицах приводятся 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.

РЕЦЕНЗИРОВАНИЕ

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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Редакция обязуется выдать Автору 1 экземпляр Журнала на каждую опубликованную статью вне зависимости от числа авторов. Авторы, проживающие в Санкт-Петербурге, получают авторский экземпляр Журнала непосредственно в Редакции. Иногородним Авторам авторский экземпляр Журнала высылается на адрес автора по запросу от автора. Экземпляры спецвыпусков не отправляются авторам.

АДРЕС РЕДАКЦИИ

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http://ojs3.gpmu.org/index.php/childmed/index.

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

М. Ф. Сухарев, С. Б. Фищев, М. Г. Рожкова

Учебник соответствует программе Министерства здравоохранения Российской Федерации по ортопедической стоматологии, предназначен и будет полезным для преподавателей курсов и стоматологических кафедр, студентов стоматологических факультетов, ординаторов, аспирантов, врачей-стоматологов.

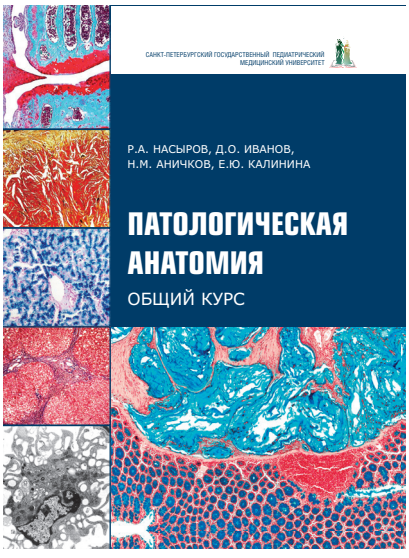
Авторы будут признательны за критические замечания и дополнения.

Твердый переплет, цветные иллюстрации, 464 страницы.

Приобрести издание можно в интернет-магазине Лабиринт:
https://www.labirint.ru/books/877708/

ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. ОБЩИЙ КУРС

Р.А. Насыров, Д.О. Иванов, Н.М. Аничков, Е.Ю. Калинина



В общем курсе патологической анатомии (клинической патоморфологии) рассмотрены вопросы общей патологической анатомии: методы исследования в патоморфологии, повреждение и гибель клеток и тканей, в том числе старение; нарушения кровообращения и иных сред организма, воспаление, репарация и регенерация, заживление ран, иммунная патология, адаптация, патология роста клеток и их дифференцировки, опухоли, генетические заболевания, учение о диагнозе в патологической анатомии, патология и факторы окружающей среды, патология, вызванная питанием, констатация смерти и др.

Учебник рассчитан на студентов-медиков всех факультетов, а также на врачей, интересующихся вопросами общей патологической анатомии.

Твердый переплет, цветные иллюстрации, 280 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
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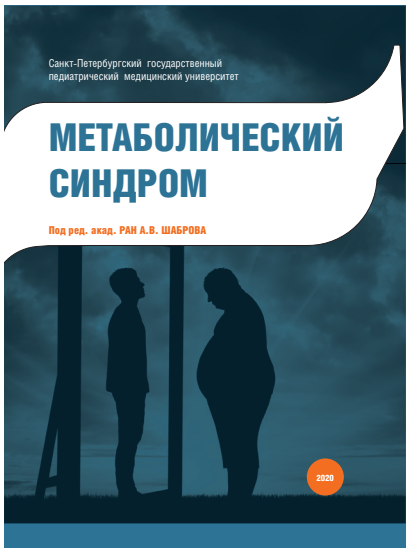
ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

МЕТАБОЛИЧЕСКИЙ СИНДРОМ

Под ред. акад. РАН А.В. Шаброва



Монография посвящена одной из ведущих проблем современного здравоохранения — метаболическому синдрому. Представлены исторические аспекты изучения метаболического синдрома и ассоциированных с ним заболеваний сердечно-сосудистой системы, критерии диагностики, эпидемиологические данные, проанализирована роль таких факторов, как микробиом кишечника, адипокины, оксидативный стресс, нарушение пищевого поведения в патогенезе метаболического синдрома. Рассмотрено влияние метаболического синдрома на бронхолегочную патологию, гастроэнтерологическую патологию, половые дисфункции. Описаны перспективные методы обследования пациентов с метаболическим синдромом, современные подходы к терапии. Монография будет интересна врачам терапевтических специальностей, научным работникам, преподавателям, аспирантам, студентам медицинских вузов.

Твердый переплет, 496 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
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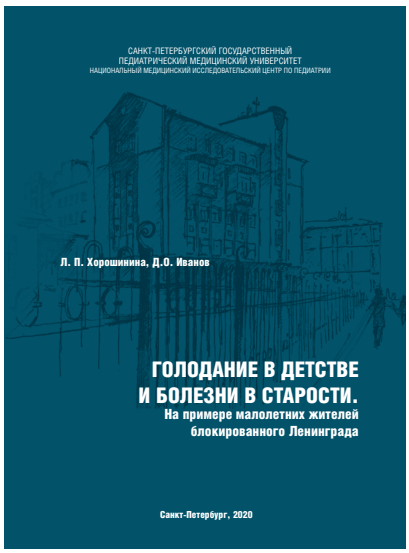
ГОЛОДАНИЕ В ДЕТСТВЕ И БОЛЕЗНИ В СТАРОСТИ

Л.П. Хорошинина, Д.О. Иванов



Книга посвящена малоизученным медицинским проблемам у людей старших возрастных групп, переживших в детстве длительные периоды голодания. Авторами изучаются отдаленные последствия длительного голодания детей и подростков в блокированном Ленинграде (1941–1944). Литературный обзор и полученные данные свидетельствуют об особенностях соматических заболеваний у бывших малолетних жителей блокированного Ленинграда, ставших ныне взрослыми. Книга переиздается повторно, текст её дополнен и исправлен.

Издание может быть интересно патологам, врачам-клиницистам, специалистам по организации здравоохранения и всем гражданам, интересующимся историей блокады Ленинграда.

2-е издание, переработанное и дополненное.

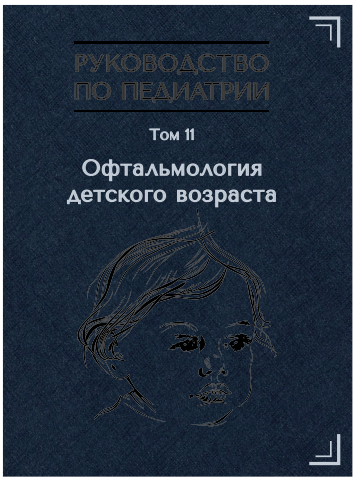
Твердый переплет, 176 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
https://www.labirint.ru/books/777647/

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА
ПРЕДСТАВЛЯЕТ

Руководство по педиатрии. ОФТАЛЬМОЛОГИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.В. Бржеский



Том 11 «Руководства по педиатрии» отражает современный уровень развития офтальмологии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний глаз у детей. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

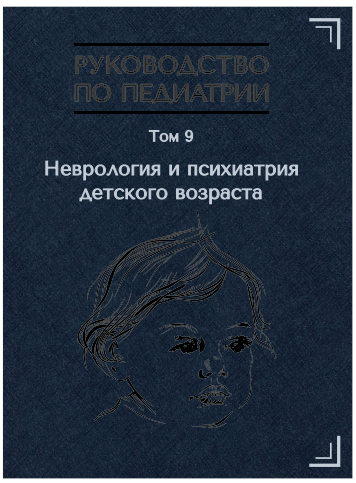
Издание предназначено офтальмологам, педиатрам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

Твердый переплет, цветные иллюстрации, 344 страницы.

Приобрести издание можно в интернет-магазине Лабиринт:
https://www.labirint.ru/books/877706/

Руководство по педиатрии. НЕВРОЛОГИЯ И ПСИХИАТРИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.И. Гузева, С.В. Гречаный



Том 9 «Руководства по педиатрии» отражает современный уровень развития неврологии и психиатрии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний нервной системы и психических расстройствах. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Руководство предназначено неврологам, нейрохирургам, психиатрам, психотерапевтам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

Твердый переплет, 288 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
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