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Варламова И.Н. (верстка)

Адрес редакции: Литовская ул., 2, Санкт-Петербург, 194100;
тел./факс: (812) 295–31–55;
e-mail: lt2007@inbox.ru

Статьи просьба направлять по адресу: lt2007@inbox.ru

Address for correspondence:
2, Litovskaya St., St. Petersburg, 194100, Russia.
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ANNIVERSARY OF THE NORTHERN MEDICAL UNIVERSITY

© Valeria I. Makarova, Anna V. Andreeva, Alexander I. Makarov, Gleb O. Samburov

Northern State Medical University. Troitsky Ave. 51, Arkhangelsk, Russian Federation, 163000

Contact information:
Valeria I. Makarova — Doctor of Medical Sciences, Professor, Head of the Department of Propaedeutics of Children's Diseases and Polyclinic Pediatrics. E-mail: arhangelsk163020@yandex.ru ORCID: 0000-002-8150-9110

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Abstract. The article presents an overview of historical documents about the 90-year history of the Northern State Medical University. The substantiation of the need to create a medical university in the European North of Russia is presented. The facts of formation, work in the war and post-war years are described in detail. A large section is devoted to the recent history of the university, achievements and plans for the future.

Key words*: history of medicine; medical university; Arkhangelsk; European North of Russia*

ЮБИЛЕЙ САМОГО СЕВЕРНОГО МЕДИЦИНСКОГО ВУЗА

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Контактная информация:
Валерия Ивановна Макарова — д.м.н., профессор, заведующая кафедрой пропедевтики детских болезней и поликлинической педиатрии. E-mail: arhangelsk163020@yandex.ru ORCID: 0000-002-8150-9110

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Резюме. В статье представлен обзор исторических документов о 90-летней истории Северного государственного медицинского университета. Представлено обоснование необходимости создания медицинского вуза на Европейском Севере России. Подробно изложены факты становления, работа в военные и послевоенные годы. Большой раздел уделен новейшей истории университета, достижениям и планам на будущее.

Ключевые слова*: история медицины; медицинский вуз; Архангельск; Европейский Север России*

INTRODUCTION

The year 2022 marks the 90th anniversary of the Northern State Medical University (SSMU), which was established in 1932 as the Arkhangelsk State Medical Institute (ASMI). Archival documents and other historical sources testify about the extremely low level of health care in the Northern Territory, formed in 1929 by uniting the Arkhangelsk and Vologda provinces, the autonomous Komi (Zyryansk) region and the islands of the Arctic Ocean and the White Sea. In 1929–1930 an All-Union census of health care institutions and medical personnel was conducted, including Northern Territory. All medical organizations regardless of departmental affiliation and all medical personnel (including private medical practitioners and unemployed doctors, as well as those in detention houses, and administrative exile) were taken into account. The census showed an acute shortage of medical personnel: 1 doctor for every 4 thousand of urban population and 1 doctor for every 18–20 thousand in the countryside. There was a critical shortage of surgeons, gynecologists, pediatricians, sanitary doctors and narrow specialists, especially otolaryngologists, ophthalmologists, phthisiologists. Unfavorable climatic

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conditions, poor transport links between the settlements of the region and the center of the country, miserable living conditions did not contribute to the consolidation of medical personnel. There was a mass departure of physicians after 1–3 years of work in the North [1].

THE BEGINNING

The Council of People's Commissars of the Russian Soviet Federative Socialist Republic (RSFSR) by its Resolution No. 1055 "On improvement of medical and sanitary services for the workers of the timber export industry of the Northern Territory" of October 2, 1931 obliged the People's Commissariat of Health to organize a medical institute in Arkhangelsk. A two-story stone building, where the Arkhangelsk City Council used to be located, was handed over to the Institute as a matter of urgency. On July 6, 1932 first preparatory courses began, and on August 4, 1932 the first director of the Institute Mikhail Yurievich Krivitsky (1896-? years, repressed; therapist, associate professor, health care organizer, the first director of Arkhangelsk State Medical Institute (ASMI)) started his work. The first and main faculty was medical and prophylactic one, additionally the faculty of working youth (Rabfak) was created. The classes began on December 16, 1932 with a lecture of Professor Mikhail Konstantinovich Zamyatin (1895-? years; doctor of medical sciences, professor, organizer and head of the normal anatomy department of ASMI in 1932–1936) on normal human anatomy. Professors from Leningrad, Kazan and other cities with medical universities were sent to Arkhangelsk to give lectures. The first teachers of ASMI were trained at the central bases, the teams of the newly established departments were actively engaged in the preparation of demonstration materials, equipped laboratories.

Organizing the teaching of clinical disciplines was a difficult problem as there were not enough clinical bases. In the early 1930s in Arkhangelsk there were functioning the City Soviet Hospital with 600 beds in ten specialized departments, the hospital of maritime transport workers, the central outpatient clinic named after V.I. Lenin, the ambulance station and emergency rooms at timber factories (prototypes of future health centers), tuberculosis sanatorium, as well as physiotherapeutic and pathological anatomical institutes. Construction of a new multidisciplinary regional clinical hospital was launched to serve as the main clinical base. During the ten-year period of its construction it changed several names (regional hospital, clinical hospital, second city clinical hospital, regional clinical hospital). The long and protracted construction of the awaited hospital was completed after the next change of administrative-territorial division of the Northern Territory and the restoration of the Arkhangelsk region in 1937, along with the Vologda region, Nenets Autonomous National District and the Autonomous Republic of Komi.

The number of students studying in ASMI increased from year to year, in 1937 there were already 920 students. The teaching staff in the first academic year consisted of only 15 full-time employees, and by 1937 it increased to 125 with 191 full-time teaching and research positions. The Institute had 14 professors with the degree of Doctor of Medical Sciences who came from Leningrad, Kiev, Kazan and Voronezh. The annual planned enrollment of students for the first year of ASMI was not always possible to fulfill, so the applicants who did not pass the competition in the medical universities of Moscow and Leningrad were enrolled. The first graduation of doctors took place in July 1937, and every fourth of 129 graduates received a diploma with honors. According to the results of the spring examination session, ASMI took the 1st place among medical universities of RSFSR and the 3rd place among medical universities of the Soviet Union. The majority of young doctors started to work independently in medical institutions of the newly formed Arkhangelsk region and the Komi Republic. In the pre-war years, the Institute continued to improve educational and methodological work, strengthening of material and technical equipment of ASMI and clinical bases in the regional center [2].

THE WAR YEARS

The international situation was alarming. The first batches of wounded and sick were delivered from the Soviet-Finnish front in the winter of 1939–1940. The Arkhangelsk garrison hospital was transformed into an evacuation hospital, where the staff, students and young scientists of ASMI were involved, among whom was the future academician Nikolai M. Amosov (1913–2002; MD, Professor, one of the pioneers and founders of Russian thoracic and cardiovascular surgery, biocybernetics, an outstanding public figure and promoter of healthy lifestyle, creator of a large school of thoracic and cardiovascular surgeons; graduated from ASMI in 1939). In 1940 Associate Professor Petr P. Erofeev (1903–1961; MD, Professor, Director of ASMI in 1940–1947) was appointed to Director of ASMI. Petr P. Erofeev was a prominent scientist, phthisiatrist, as well as an excellent organizer of

health care and higher education during the difficult years of the Great Patriotic War. During the war period ASMI faced a difficult task: the forced reduction of the term of study and the number of teachers to maintain the achieved high level of educational process and quality training of doctors. With the beginning of the war the academic year in ASMI began on August 1, 1941. According to the new curriculum students of the II course had to complete their studies at the Institute in March 1944, and those studying at the III course — in February 1943. In June 1941, 196 doctors trained according to the pre-war curriculum were graduated, and in December of the same year — the second graduation of 208 students taught according to the shortened curriculum. The shortened training period for medical students had a negative impact on the quality of training of graduates. Awareness of this fact by the top leaders of medical education led to the restoration of pre-war curricula and programs in accordance with the order of the All-Union Committee for Higher School Affairs of June 19, 1942. This order clearly regulated the arrangement of credits and examinations.

Studying was difficult. Students, half-starved and even straving, as well as all residents of Arkhangelsk in that war time, often weared coats in cold lecture halls while listening and writing down lectures on sheets of technical paper and newspapers, dipping pen pens in ink pots that they carried with them. In practical classes they mastered laboratory studies of blood and other biological materials, studied human anatomy (there were enough corpses). In hospitals they studied methods of examination of patients with diseases and injuries. When they had free time, medical students (and they were mostly girls) unloaded echelons with the wounded, carried and transported them across the Northern Dvina on the ice in winter, worked as nurses and orderlies, donated blood, although they lived on hunger. At night they went out to work with talmans in the seaport to account for unloaded military equipment and cargoes delivered on the ships of the allied northern convoys. Ships were moored in the right bank port of Bakaritsa and the left bank deep-water port area of Ekonomiya, to which there were no railroad tracks. In the pre-war period the Northern Railway connecting Arkhangelsk with the center ended on the right bank in the districts of Bakaritsa and Pirsy.

In 1941, the Soviet army was primarily lacking tanks, airplanes, explosives, which were to be urgently sent to all fronts, and first of all — to the combat units defending Moscow. The students of ASMI were assigned a task — to take part in the construction of a narrow gauge railroad connecting the port district of Ekonomiya with the crossing to the left bank of the Northern Dvina. 300 students in severe winter conditions of 1941–1942 selflessly worked on the construction of the narrow gauge railroad, laying sleepers and rails. The task was completed ahead of schedule. Some of the students were engaged in collecting firewood for the educational building and dormitory. The others were on duty on the attics and roofs of buildings during German air raids and bombing of Arkhangelsk, showing courage and heroism in extinguishing incendiary bombs. In 1941, teachers and students of ASMI transferred bonds for 70,000 rubles to the USSR Defense Fund, continuing to deduct money for the front needs on a monthly basis. During the war years they transferred 257,000 rubles for the construction of a squadron and a tank column. Hunger and cold, unsanitary conditions, lack of disinfectants led to outbreaks of infectious diseases among the civilian population. Typhoid fever and typhus, measles and dysentery were brought to the Arkhangelsk region and the regional center by immigrants from other regions, sent for logging and fishing. Brigades of students went around residential houses and hostels, enterprises and various organizations, where they fought against unsanitary conditions, carried out anti-epidemic measures and sanitary-educational work. Unfortunately, during the hardest war period students of the medical institute were ill with alimentary dystrophy, hypovitaminosis, infectious and other diseases; some of them died before realizing their dream — to become a doctor. In total, 943 people graduated from ASMI during the war years, more than 300 of them were called up to the warring units of the land forces and naval fleets after graduation.

During the Great Patriotic War a powerful hospital base of the Karelian Front was deployed in the Arkhangelsk region. In order to improve treatment and diagnostic work in evacuation hospitals, the staff of clinical departments of ASMI worked as consultants. Professors were members of the hospital council of the Arkhoblzdravotdel (department under the Commissariate of Health in Arkhangelsk region). The employees of ASMI Georgy Andreevich Orlov (1910–1986; doctor of medical sciences, professor, head of the chair of general surgery of ASMI in 1944–1981; creator of the largest scientific and practical school of surgeons in the European North of Russia) and Faina Ignatyevna Sharapova (1913–1968; PhD in medical sciences, associate professor, head of the chair of general surgery of ASMI in 1944–1981) had senior positions in evacuation hospitals.

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Prof. G.M. Davydov, who came from besieged Leningrad, was appointed chief surgeon of the Arkhangelsk region and scientific adviser of the regional blood donor service in 1942. He was repeatedly sent to district hospitals to perform surgical operations on recruits to the front-line armies. Nethertheless, research work continued at the medical institute. The annual scientific sessions were attended by the staff of ASMI, doctors of evacuation hospitals and hospitals of the regional center, as well as senior students. The staff of ASMI developed new surgical interventions and medical technologies that allowed saving the lives and restoring health of many defenders of the homeland and civilians [3].

The staff of ASMI provided great assistance to civil healthcare, including evacuees. Professor Maria Vladimirovna Pikkel (1911–2008; Doctor of Medical Sciences, Professor, Head of the Department of Pediatrics of ASMI in 1966–1988) wrote in her memoirs: "Immediately after the opening of the Ladoga "Road of Life" from Leningrad, children and teenagers began to come to us. Among them was the son of writer Yuri German, who died a day later in my isolation unit... Arkhangelsk children were not much better. Among them there were 4 or 5 children with noma in the isolation unit. This disease was also called "water cancer", and the word "cancer" in this disease did not meant its true malignant nature, but their imminent death. There were no uncontrollably multiplying cells, but on the contrary — uncontrollable decay of tissues under the influence of special putrefactive bacteria in the complete absence of defense of the child's body. The picture of the disease in all these children was terrible. Fortunately, they did not come in all at once — no more than two children at the same time. I treated these extremely emaciated patients for a very long time. They were fed with great difficulty. It is difficult to describe the struggle for their lives. I came up with the idea to start treating them with blood transfusion and and new sulfidine which had just appeared at that time, it was active against many untreatable infections... This treatment was very effective — not a single child died, although recovery was slow — it lasted for several months" [4].

The most important inventions and new medical technologies of ASMI employees in 1941–1945 were honored with awards. Thus, chemist, associate professor A.I. Vedrinsky was the first in ASMI to be awarded after the invention of non-freezing ointment for artillery gun sights (based on alginic acid from White Sea algae). In co-authorship with surgeon Prof. G.A. Orlov he also invented "Algotan" ointment for treatment of thermal burns on the basis of algae. Other scientists of ASMI together with algologists also implemented the results of research in practice, including in the food industry (bread, povidlo, etc.). In addition to algae, other natural organic components were actively introduced into practice. The method of Israel Isaakovich Matusis (1910–1975; doctor of medical sciences, professor, biochemist, scientist-vitaminologist, head of the Department of Biochemistry of ASMI in 1939–1949) for obtaining dehydrated concentrate of vitamin C from pine needles without the use of activated carbon, as well as his technology in co-authorship with M.D. Kiverin for the production of extracts from pine needles were in demand. Northern medicinal plants were widely used for the manufacture of medicines. The staff of ASMI passed the severe military trials with honor. The motherland highly appreciated the heroic work of the staff during the Great Patriotic War [5].

THE POST-WAR PERIOD

The war was followed by a succession of new heads of the university. In 1947, Associate Professor Sergei Nikolaevich Gildenskiold (1899–1974; military doctor, Ph.D of Medical Science., associate professor, director of ASMI in 1947–1952) was appointed to the post of director of ASMI; subsequently, in 1952 — Professor Ivan Nikitich Matochkin (1899–1973; Ph, Professor, Head of the Department of Normal Anatomy of ASMI), in 1953 — Alexander Andreevich Kirov (1913–1977; Doctor of Medical Sciences, Professor, Head of the Department of Hospital Surgery of ASMI in 1971–1977), a graduate of ASMI, Associate Professor. In 1958 the Faculty of Stomatology was opened in ASMI. The first dean was Associate Professor Ivan Vasilievich Vishnevsky (1905-?; Candidate of Medical Sciences, Associate Professor, Head of the Department of Surgical Stomatology of ASMI in 1960–1962, organizer of the Faculty of Stomatology of ASMI). Subsequently there were established following departments: in 1960 — the Department of Orthopedic Dentistry (first head — Associate Professor L.N. Kaftasieva); the Department of Therapeutic Dentistry (first head — V.M. Kukanov); the Department of Maxillofacial Surgery and Surgical Dentistry (first head — Associate Professor I.V. Vishnevsky).

A real breakthrough in Arkhangelsk dentistry was coming, outpatient clinics were built. In 1961 Ivan Gavrilovich Chernetsov (1904–1978; therapist, Candidate of Medical Sciences, Associate Professor, Rector of ASMI in 1961–1963) was appointed Rector of ASMI, 2 years later he was re-

placed by Victor Demjanovich Dyshlovoy (1928–2011; Doctor of Medical Sciences, Professor, Head of the Department of Pathophysiology of ASMI in 1963–1966, Rector of ASMI in 1963–1965). Each head made his significant contribution to the development of the university, but their frequent change was not useful.

In 1965 a bright page in the annals of ASMI began, which was headed by the graduate of ASMI Associate Professor Nikolay Prokopyevich Bychikhin (1927–1987; surgeon, promoter of higher medical education, medical science and public health in the European North of the Russian Federation, Doctor of Medical Science, Professor, Head of the Department of General Surgery of ASMI in 1981–1987). Under the leadership of Nikolay Prokopievich many new directions in Arkhangelsk medicine were developed. He led ASMI for 22 years, he passed away early, the book "A worthy son of the Fatherland" was written about him. Under the leadership of the new rector the laboratory for studying the problems of human acclimatization in the Far North (the head — PhD in medical sciences N.P. Neverova) was created. In 1960s the Faculty of Public Professions with two-year term of study was opened in ASMI, the first student construction team was created. Much attention is paid to the fight against tuberculosis, thus, the Department of Phthisiopulmonology is founded (the first head — Associate Professor A.R. Shevchenko). In 1969 the institute newspaper "Medic of the North" was launched, in 1970 the Council of Young Scientists was established. During this period "Search" studio-theater was created in ASMI, later it was the winner of the Lenin Komsomol Prize of the Central Committee of Komsomol and Arkhangelsk Regional Komsomol Organization (permanent head of the studio — Y.L. Pacevich, 1946–2012; Doctor of medical sciences, professor, corresponding member of the Academy of Social Sciences, Honored Worker of Culture of the Russian Federation). In 1970s new subdivisions were created in ASMI, which quickly became powerful structures: 1971 — the Department of Traumatology, Orthopedics and Military Surgery (the first head — Dr. M.Sc., Professor Vladimir Fedorovich Tsel, 1898–1974; Dr. M.Sc., Professor, Head of the Department of Hospital Surgery of ASMI in 1959–1971, Department of Traumatology, Orthopedics and Naval Surgery of ASMI in 1971–1974), 1975 — the course of anesthesiology and resuscitation, later — the Department of Anesthesiology and Resuscitation (the head — PhD in Medical Sciences, associate professor Eduard Vladimirovich Nedashkovsky, D.M.Sc., professor, founder and first head of the Department of Anesthesiology and Reanimatology of ASMI, honorary President of the Association of Anesthesiologists and Reanimatologists of the North-West of Russia), 1978 — the Department of Pediatric Dentistry (first head — associate professor Pavla Grigorievna Knyazeva, 1929–2016; PhD in medical sciences, Assistant of the Department of Therapeutic Dentistry of ASMI, Head of the course of pediatric dentistry in 1976–1986).

THE PEDIATRIC FACULTY

In 1977 the Pediatric Department was established as part of the Faculty of Medicine, which in 1979 received the status of the Pediatric Faculty. The first dean — Associate Professor Valery Aleksandrovich Kudryavtsev (1941–2001; pediatric surgeon, honored doctor of the Russian Federation, the first chief pediatric surgeon and organizer of pediatric surgery service in Arkhangelsk and the whole region) — was a legendary person, the book about whom was written [6]. The basis of the new faculty was the Department of Pediatric Diseases of the Faculty of Medicine. Since 1935, under the leadership of the first heads (graduates of the Kazan Pediatric School, Professor Y.V. Makarov and Associate Professor A.G. Suvorov) it had accumulated a great educational, methodological and scientific experience. The Department of Pediatric Diseases of the Faculty of Medicine received the status of the Department of Pediatrics of the Faculty of Pediatrics (the first head — Professor M.V. Pikkel, later — Professor V.A. Ternovskaya, Associate Professor A.Y. Trubina and Professor S.I. Malyavskaya). Owing to the work and organizational talent of V.A. Kudryavtsev, the faculty was rapidly gaining strength, its personnel potential was growing, new pediatric departments were opened. Many teachers were awarded governmental awards, honorary title "Honored Doctor of the Russian Federation" for their conscientious, active and fruitful work. In the jubilee year 1982, the year of 50th anniversary of ASMI, the Department of Pediatric Surgery was established, which was headed by Candidate of Medical Sciences, Associate Professor V.A. Kudryavtsev, being the permanent chief pediatric surgeon of the Arkhangelsk region and chief physician of the Children's Regional Clinical Hospital since its opening in 1972. In 1987 he was also elected rector of ASMI. In the late 1980s — early 1990s new departments were actively created in ASMI, among them: the Department of Propaedeutics of Pediatric Diseases and Polyclinic Pediatrics (headed by Professor V.I. Makarova),

the Department of Pediatric Infections (headed by Professor L.V. Titova), the Department of Neonatology and Perinatology (headed by Professor G.N. Chumakova), the Department of Polyclinic and Social Pediatrics (headed by Professor L.I. Menshikova).

The first graduation of pediatricians took place in 1983. In the final act of the state examination commission, the chairman of which was the most famous pediatrician in the country, Professor Nikolai Pavlovich Shabalov, it was noted that graduates had high quality of training, which is as good as in the experienced Leningrad Pediatric Institute. Over the years of its existence the faculty has trained more than 3000 pediatricians. Most of them work in cities and districts of the North-West of Russia. The best graduates of the faculty have shown themselves as organizers of practical healthcare, others have become teachers of pediatric departments of their alma mater, and others work as physicians in other regions of Russia and abroad [7].

SCIENTIFIC PEDIATRIC SCHOOL

Scientific schools in medicine have always existed. They have brought teachers and students together through common scientific and clinical research. Pediatrics is a relatively young science when compared to, for example, surgery, internal medicine or obstetrics. And scientific research in pediatrics does not have a very long history either. What determined the emergence of scientific pediatric school in the Russian North? First of all, of course, a person — Maria Vladimirovna Pikkel, the first woman professor in the European North of Russia. Maria Vladimirovna's scientific activity began with the study of rickets and dystrophy in children in the difficult post-war years. Then there was a doctoral dissertation devoted to the problem of tuberculous meningitis in children. Prof. M.V. Pikkel by her life and professional skill managed to prove that science is impossible without medical practice. She awakened interest in pediatrics in many people; a team of like-minded people began to form around her and a pleiad of students and followers grew up. The first dissertations under the guidance of Maria Vladimirovna were defended by V.N. Koroleva, T.I. Mugandina, V.D. Novozhilova, V.A. Ternovskaya. They were different in topics, but they were united by one idea — peculiarities of child's health living in the North. The birth of the Pediatric Faculty, training of scientific personnel through postgraduate studies at the Leningrad Pediatric Institute and the 1st Moscow Medical Institute allowed the pediatric departments of the Arkhangelsk Medical Institute (Academy, University) headed by the pupils of Prof. M.V. Pikkel (Prof. V.A. Ternovskaya, Prof. V.I.Makarova,Prof.L.V.Titova,Prof.G.N.Chumakova, Prof. E.N. Sibileva, Prof. V.A. Kudryavtsev, Prof. N.D. Shiryaev, Dr. I.A. Turabov) to strengthen and raise the next young generation of researchers, who also devote their scientific research to the study of children's health in the European North of Russia, the peculiarities of the clinical course of diseases, offer new methods of diagnosis, treatment and prevention [7].

Medical institutions, which are the bases of pediatric departments, have a full range of modern diagnostic and treatment equipment. In addition, children's outpatient clinics, preschool institutions, schools, regional and city children's homes are used for the educational process. Therapeutic work is an integral part of teachers' activity of the specialized departments. The teaching staff works in hospitals, conducts outpatient treatment. Assistants of the departments hold on-call surgeries, consultations, seminars. Professors and associate professors supervise pediatric care in the districts of the region, carry out visiting consultative work. Many of them are chief freelance specialists of the Arkhangelsk region. They actively participate in the organization of scientific-practical conferences, in the attestation work of the Ministry of Health of the region. Clinical residents are trained at the departments. Teachers of the departments give lectures and conduct classes at the Faculty of Professional Development and Professional Training of Specialists.

Scientific researches are carried out within the framework of the Russian scientific and technical programs "Health of the population of the European North" and "Children of the North", as well as several international scientific projects: the program on neuropsychopharmacology (Prof. V.A. Ternovskaya), the Barents-region program on diphtheria and vaccine prevention (Prof. L.V. Titova), the program "Decade of musculoskeletal diseases" (Prof.

V.I. Makarova, Associate Professor I.V. Babikova), the program on pediatric urology (Prof. N.D. Shiryaev, Associate Professor N.V. Markov), the program on breastfeeding (Prof. G.N. Chumakova), the program on in vitro fertilization (Prof. A.L. Zashikhin and Prof. A.L. Zashikhin and Y.V. Agafonov), the program "Bronchial asthma and allergy in children" (Prof. V.I. Makarova, Associate Professor A.K. Kopalin), the program on pediatric oncohematology (Dr. I.A. Turabov). Looking at the world map, the geography of sci-

entific presentations by pediatricians of ASMI is quite extensive: Norway, France, Canada, Austria, Turkey, Bulgaria, USA, Italy, Greece, Poland, Germany, Israel, Japan, Sweden, Holland. Many projects are still being implemented together with the leading scientific centers of Russia: National Center for Disease Control of the Russian Academy of Sciences, Moscow Institute of Pediatrics and Children's Surgery of the Ministry of Health of the Russian Federation, Institute of Rheumatology of the Russian Academy of Sciences, Institute of Nutrition of the National Center for Disease Control, Moscow Regional Research Clinical Institute named after M.F. Vladimirsky, Moscow Research Institute of Epidemiology and Microbiology named after G.N. Gabrichevsky, Children's Research and Clinical Center of Infectious Diseases of FMBA (St. Petersburg), St. Petersburg Pediatric Medical University and others.

MODERN HISTORY OF THE UNIVERSITY

In 1982 by the Decree of the Presidium of the Supreme Soviet of the USSR ASMI was awarded the Order of the Red Banner of Labor. The first computing center is opened in the university with the support of the most famous graduate — Academician N.M. Amosov. Prominent scientists, who graduated from the university in different years, including graduates of the war years, gathered at the solemn meeting devoted to 50th anniversary of the ASMI, among them -General Nikolai Mikhailovich Rudny (1920–1993; participant of the Great Patriotic War, chief of infirmary, senior doctor of the Normandy-Neman regiment, head of the Air Force Aviation and Space Medicine Service in 1974–1988), Colonel Ivan Ivanovich Kasyan (1920–1990; leading doctor, senior researcher of the Institute of Aviation and Space Medicine in 1961–1975), since 1975 — deputy head of the group of medical support of flights in the Central Control Center. Ivan I. Kasyan was engaged in the study of weightlessness problems, he personally participated in 420 flights on the Tu-104A laboratory airplane to study the condition and performance of humans in short-term weightlessness). It bears emphasis that many other graduates of ASMI also contributed in making the Arkhangelsk scientific medical school famous far beyond the region.

In 1991, the Faculty of Social Workers was opened in ASMI, education of foreign students began, the first dissertation council in Russia was opened to defend doctoral dissertations in the new specialty "Safety, protection, rescue and life support in emergency situations" (medical and biological sciences) and in the specialty "Physiology" (medical sciences). In 1996, the dissertation council for the defense of dissertations in clinical specialties "Internal Medicine", "Surgery" and "Pediatrics" began its work.

In 1993 Prof. Pavel Ivanovich Sidorov was elected rector of ASMI. Active international cooperation began under his leadership including the exchange of students (Norway), creation of the Russian-German Center of Positive Psychotherapy and the Swedish-Russian Social College. A department of international cooperation is created in ASMI. In 1994 ASMI is reorganized into Arkhangelsk State Medical Academy (ASMA). The Northern Scientific Center of Russian Academy of Medical Science is organized on the basis of ASMA, the first issue of the scientific journal "Human Ecology" is published (founders of RAS and RAMS). In 1995, the Faculty of Advanced Training and Professional Retraining of Specialists was opened in ASMA, and in 1996 — doctoral studies. In 1997 the faculties of clinical (medical) psychology and medical managers (nurses with higher education) were established in ASMA. The North-West Branch of RAMS on the basis of St. Petersburg Bureau and Northern Scientific Center was organized in ASMA in 1998. The Institute of Management and the Faculty of Medicine and Preventive Medicine are opened. The Center of Information Technologies is established. ASMA is officially recognized as the center of medical science and medical education in the European North of Russia. Institutes of public health and social work, hygiene and medical ecology, psychology and psychiatry are created in the structure of the university. The Department of Economics and Management was established on the basis of the Institute of Management of ASMA.

In 2000, ASMA was reorganized into the Northern State Medical University, University Lyceum, Severodvinsk Institute of Medical Education, International Faculty of General Practitioner, Faculties of Ecology and Pharmacy, Russian-Norwegian Center of In Vitro Fertilization are established.

In 2001, the Institute of Information Technologies and the Faculty of Adaptive Physical Culture were opened in NSMU.

Institutes of Family Medicine and Clinical Physiology were established. For the first time in the history of the university, in 2002, courses of nurses of mercy were opened under the patronage of Metropolitan Tikhon of Arkhangelsk and Kholmogorsk. A year later the Society of Orthodox Physicians was formed in NSMU. In 2003 the Research Institute of Polar Medicine, the Research Institute of Marine Medicine, the Department of Pedagogy and Psychology were established

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in NSMU. In 2006 the Arkhangelsk International School of Public Health started its work in NSMU, where scientists from various countries were able to teach students. In 2008 the University became a laureate of the contest "System of quality graduate training in educational institutions of professional education". In 2005, a museum complex was established in NSMU. The Society for the Study of the History of Medicine of the European North (currently named after its founder, Prof. G.S. Shchurov) was established on its basis. There had been developed the design concept of memorial classrooms. A memorial sign dedicated to the medics of the war years was installed. Within a year the named classrooms were opened in the university. In 2009 the museum of the history of medicine of the European North was opened in NSMU. It presents the chronicle of the university and the development of northern scientific schools. The museum complex of NSMU was awarded the memorable medal "70 Years of Victory in the Great Patriotic War of 1941–1945" by V.V. Putin for its active participation in patriotic education of citizens and solution of social and economic problems of veterans of the Great Patriotic War. Moreover, museum complex of NSMU was awarded with the Honorary sign "For active work on patriotic education of citizens" by the board of the Russian State Military Historical and Cultural Center under the Government of the Russian Federation, as well as with the Commemorative sign "Dervish-75" for the great contribution to the preservation and popularization of the history of allied northern convoys, as well as to patriotic education and training of citizens (youth) to serve the Fatherland.

Much attention was paid to sports training and patriotic education of future physicians.

In 1980 the national team of skiers of ASMI won the title of the champion among the teams of medical universities of the USSR. Great awards were given to skaters. Yachtsmen, swimmers, track and field athletes, weightlifters, boxers, wrestlers and other athletes were the sports pride of ASMI. Many of them became famous scientists, some of them work in the university until now. The Department of Mobilization Training and Disaster Medicine was established on the basis of the previously functioning departments of military sanitary training (1936–1949), military medical training (1949–1955), naval training (1955–1993), military and extreme medicine (1993–2009); the head of the department is Professor Y.E. Barachevsky. For the last 10–15 years, on the threshold of the 90th anniversary, new bright pages in the history of the University have been written. During this period the WHO launched pilot project in NSMU studying the impact of global warming on human health. Several employees of the University became WHO expert-consultants. Consequently, NSMU took part in implementation of the international project (6 countries) "Lifelong Learning System for Medical School Teachers" within the framework of TEMPUS IV. General agreement on cooperation with the Faculty of Medicine of the University of Tromsø and University Hospital of Northern Norway for 2010–2013 was signed in Tromsø (Norway). In 2011 the university passed the certification of quality management system according to ISO 9001:2008 standardization. Among the significant events were the establishment of the Northern Branch of the Academy of Polar Medicine and Extreme Human Ecology, as well as the Department of Clinical Pharmacology and Pharmacotherapy (Prof. N.A. Vorobyova). The Social Faculty of Mental Health named after St. Luke (V.F. Voyno-Yasenetsky) was opened and became the first faculty of that kind in Russia. A year later a lecture hall as named after St. Luke.

In 2014, Dr. L.N. Gorbatova (Head of the Department of Pediatric Dentistry) was elected Rector of NSMU.

The recent history of the University is rich in events. In 2016. NSMU became a member of the National Arctic Scientific and Educational Consortium, which nowadays unites 38 organizations: 14 universities, 16 research centers and 8 organizations of the real sector of the economy. The Association of ASMI-ASMA-NSMU graduates was established; the new organization united over one and a half thousand members. A cooperation agreement was signed between NSMU, LLC "ExoAtlet" and the Development Corporation of the Arkhangelsk region. The project "Recognize Your Heart" was launched. Accreditation and Simulation Education Center was established. NSMU was honored with the regional public award "Heritage of the North". In March 2017. NSMU hosted participants of the Arctic Municipalities Forum — the first platform of the IV International Arctic Forum. Artur Chilingarov, State Duma deputy, Special Representative of the President of the Russian Federation for International Cooperation in the Arctic and Antarctic, took part in this Forum. In April 2017, the museum complex of NSMU was awarded a special diploma in the nomination "Defenders of the Fatherland" within the framework of the regional contest "Book of the Year -2016" for the book "Graduates of the Arkhangelsk State Medical Institute in the war years, 1941–1944". In 2018, Northern State Medical University

signed cooperation agreements with territorial funds of compulsory medical insurance, territorial bodies of the Federal Service for Supervision of Health Care (Roszdravnadzor), state authorities in the field of health protection of the Arkhangelsk and Murmansk regions, the Komi Republic and the Nenets Autonomous District within the framework of the federal project "Higher Education Institutions-Region". Information interaction between the participants of the project "University-region" is provided by the Project Office for the development of regional health care.

In 2018–2022 the Project Office organized a series of field events with the participants of the project "University-region" in order to implement federal projects "Development of the system of primary health care", "Provision of medical organizations of the health care system with qualified personnel".

In 2021 the interdepartmental project "Digital Department" was launched in order to create a professional retraining program "Digital Technologies in Healthcare". Studying this program gives students the opportunity to obtain additional qualifications. 108 students took the course on the basis of Innopolis University and started training. In 2022, under the terms of co-financing of the University and the administration of the Arkhangelsk region, a student training and experimental surgical unit will be created, which will be included in the structure of the Federal Center for Accreditation and Simulation Training. The interdepartmental student surgical association "Ligature" will continue its work on the basis of the operating unit, contributing to the development of surgical skills of students. Participation in the competition "Priority-2030" became one of the key achievements of the University. According to the results of this competition NSMU became one of 15 universities recognized as candidates for participation in the program. This allowed the university to move dynamically towards the development of the scientific component: the consortium "Arctic Medicine" was created, 22 projects were developed (10 of which have already been implemented). The additional professional program "Digital Technologies in Healthcare" was launched. In order to implement programs of academic strategic leadership "Priority-2030" and principles of state policy of the Russian Federation in the Arctic until 2035 (paragraph 266 of the Unified Action Plan) as well as to ensure national security for the period until 2035 (order of the Government of the Russian Federation on April 15, 2021 № 996-r), the creation of a federal center of Arctic medicine is envisaged.

Currently, more than 4.5 thousand students study at the university and 6 to 8 thousand doctors improve their qualification per year. Training of specialists with secondary professional education is carried out on 5 programs. Educationn at the university is performed at all levels of higher education: bachelor's degree, specialty, master's degree; training of personnel of higher qualification: postgraduate studies, residency. Today the university trains medical personnel for 30 regions. The educational and scientific activities of the university are focused on the problems of the Arctic and subarctic territories. The University has managed to achieve high indicators in international scientific and educational activities, which allowed to strengthen its competitive advantages. Currently, 1380 international students from 12 countries are studying at SSMU [8].

"We have passed a serious way from a medical school to a university and, undoubtedly, we can be proud of the fact that all these years the university kept the course on quality education. Speaking about the achievements, first of all, it is worth saying that they would be impossible without the teaching staff, employees of various departments — all those who worked in different years and continue to work today. It is difficult to single out the main achievements of the university, because at each stage of its development there were its own tasks and requirements. Every year the infrastructure was improved, the list of specialties and the number of students grew, the material base was strengthened," said Rector Lyubov Nikolaevna Gorbatova at the solemn meeting dedicated to the anniversary [9].

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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MODERN DATA ON THE INTESTINAL MICROBIOME AND THE STAGES OF ITS FORMATION

© Natalia M. Bogdanova

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Natalia M. Bogdanova — Candidate of Medical Sciences, Associate Professor of the Department of Propaedeutics of Children's Diseases with a Course in General Child Care. E-mail: natasha.bogdanov@mail.ru ORCID: 0000-0002-4516-4194

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Abstract. The human microbiome is a collection of microorganisms, mainly bacteria, that inhabit the human body. In today's world, the relationship of a macroorganism with intestinal microbes is the result of evolution over a lifetime of thousands of generations. In recent years, due to metagenomic analysis, about 240 new species of microorganisms of the gastrointestinal tract have been isolated and described, many of which have not yet been cultivated. In the process of evolution, microorganisms adapt to environmental conditions and acquire an increased ability to reproduce. Despite the use of genomic technologies, the issue of microbial colonization of the fetus remains debatable. It has been established that the microbiome (odontogenic, intestinal, vaginal) of the mother and the sanitary state of the environment determine the nature of the primary colonization of the child. Subsequently, the composition of its intestinal microbiota largely depends on the nature of feeding. The human milk microbiome is quite complex, dynamic and changeable throughout lactation. The gut microbiota of a breastfed infant is characterized by a high population level of infant bifidobacteria species (90%) and a low content of *C. difficile* and *E. coli*. The introduction of complementary foods modifies the bacterial diversity in the baby's intestines. It is shown that the composition of the intestinal microbiota of the child is significantly influenced by the place of residence and visits to the children's institution. Thus, the formation of the intestinal microbiome is a long, complex multifactorial process, the violation of which is associated with the development of various pathological conditions in the child's body. Understanding the mechanisms of microbiome development will allow developing effective methods for the prevention and correction of microecological disorders in a child and related diseases in different periods of life.

Key words: *microbiome; fetus; meconium; intestines; breast milk; infant*

СОВРЕМЕННЫЕ ДАННЫЕ О КИШЕЧНОМ МИКРОБИОМЕ И ЭТАПЫ ЕГО ФОРМИРОВАНИЯ

© Наталья Михайловна Богданова

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Наталья Михайловна Богданова — к.м.н., доцент кафедры пропедевтики детских болезней с курсом общего ухода за детьми. E-mail: natasha.bogdanov@mail.ru ORCID: 0000-0002-4516-4194

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Резюме. Микробиом человека — совокупность микроорганизмов, преимущественно бактерий, населяющих его организм. В современном мире отношения макроорганизма с кишечными микробами — результат эволюции на протяжении жизни тысячи поколений. За последние годы благодаря метагеномному анализу выделено и описано около 240 новых видов микроорганизмов желудочно-кишечного тракта, многие из которых еще не культивированы. В процессе эволюции микроорганизмы адаптируются к условиям окружающей среды и приобретают повышенную способность к размножению. Несмотря на

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использование геномных технологий, вопрос о микробной колонизации плода остается дискуссионным. Установлено, что микробиом (одонтогенный, кишечный, влагалищный) матери и санитарное состояние окружающей среды определяют характер первичной колонизации ребенка. В последующем состав его кишечной микробиоты во многом зависит от характера вскармливания. Микробиом грудного молока довольно сложен, динамичен и переменчив на протяжении лактации. Кишечная микробиота ребенка, получающего грудное молоко, характеризуется высоким популяционным уровнем младенческих видов бифидобактерий (90%) и низким содержанием *C. difficile* и *E. coli*. Введение продуктов прикорма модифицирует бактериальное разнообразие в кишечнике малыша. Показано, что на состав кишечной микробиоты ребенка значительное влияние оказывает место проживания и посещение детского учреждения. Таким образом, формирование кишечного микробиома является длительным, сложным мультифакторным процессом, нарушение которого ассоциируется с развитием различных патологических состояний в детском организме. Понимание механизмов развития микробиома позволит разработать эффективные методы профилактики и коррекции микроэкологических нарушений у ребенка и связанных с ними заболеваний в разные периоды жизни.

Ключевые слова: *микробиом; плод; меконий; кишечник; грудное молоко; младенец*

INTRODUCTION

One of the most important scientific discoveries made in the first decade of the 21st century is the revelation of the human microbiome (microbial community), that is, the combination of microorganisms (mainly bacteria) inhabiting the human body. For this reason, the frequently used phrase "human microflora" is not quite correct given the current knowledge. It has been proved that our organism is not just a set of microorganisms, but a real biome — microbiome. The microbiome is in a complex equilibrium with the macroorganism, and their synergistic interactions remain an object of intensive research.

In the modern world, the relationship between the macroorganism and gut microbes is the result of evolution over thousands of generations. For millions of years, evolution has acted both on our 23,000 genes, and on nearly 4 million genes (both human and microbial) that are present both in and on our bodies [1].

Advances in genomic approaches, including phylogenetic marker-based microbiome profiling and shotgun metagenomics have made it possible to describe the composition of the microbiota during phylogeny and the numerous associations between its composition and disease [2, 3]. Shotgun metagenomics is a technique used to sequence many cultured microorganisms and the human genome by randomly cutting DNA, sequencing multiple short sequences, and reconstructing them into a coherent sequence.

Metagenomics provides access to characterize the microbiota at the taxonomic level and at the level of putative functions encoded by numerous microbial genes, but unfortunately it does not provide precise phylogenetic information.

In the last decade, about 240 new species of gastrointestinal (GI) microorganisms have been discovered and described through metagenomic analysis, many of them not yet cultured. Integration with culturing approaches is needed to fully understand the function of the intestinal ecosystem in relation to health and disease.

Systems biology allows us to consider functional analysis of the microbial community, i.e. to perform quantification of metabolic activity through the measurement of RNA by metatranscriptomics [4], proteins by metaproteomics [5] and metabolites by metabolomics. The use of these methods is essential to better understand the molecular mechanisms involved in both symbiosis and dysbiosis.

EVOLUTIONARY PATHWAY OF THE MICROBIOTA

Increasing evidence suggests that shared evolutionary history influences both the microorganism and the surrounding and internal microcosm.

Bacteria originated about 3.8 billion years ago, and the eukaryote lineage, which includes humans, evolved after the oxygenation of the Earth's atmosphere, 2.2–2.4 billion years ago [6, 7]. For a long time, bacteria together with archaea, protists (unicellular organisms belonging to eukaryotic cells) and fungi remained free-living single cells, although some became host-associated, i.e. acquired interspecific forms of coexistence (parasitism, mutualism, commensalism, neutralism, etc.).

In the process of natural selection, microorganisms adapt to environmental conditions and acquire increased adaptability — the ability to reproduce.

The phylogeny of homo sapiens was accompanied by repeated changes in the environment and the nature of nutrition — the main factors of selective pressure (reproductive success), leading to

the reforming of its genome. A prime example is the impact of starvation. The human genome contains adaptive markers that ensure survival under starvation, but the accommodations of the human microbiome that offer energy-saving traits for the human host remain unknown [8, 9].

Along with microbiome representatives, the host immune system evolved to regulate and prevent microbial contamination of tissues, organs and body systems. In the course of evolution, the host immune system, in parallel with its microbiome, has developed sophisticated mechanisms to identify and destroy invading microbes, whether they are microbiome representatives or primary pathogens invading forbidden territories [10].

Environmental reorganization and urbanization lead to maladaptation of the microbiome and immune response, negatively affecting health and causing dangerous diseases.

DIVERSITY OF THE HUMAN MICROBIOME

The microbiome in our body is distributed inhomogeneously. According to its topography and species composition it is possible to distinguish: the microbiome of the skin, oral cavity, respiratory tract, urogenital tract and intestine — the largest microbiome of our body. Each millimeter of the colon is colonized by approximately 1011 microbial cells compared to 108 cells in the small intestine [11].

Currently, more than 1000 species of intestinal bacteria have been characterized. Culture-dependent and independent methods estimate that between 150 and 400 microbial species reside in the intestine of each individual [12]. Most of these species belong to *Bacteroidetes* types (genera *Bacteroides* and *Prevotella*), *Firmicutes* (genera *Lactobacillus, Clostridium, Eubacterium* and *Ruminococcus*), *Actinobacteria* (genera *Bifidobacterium* and *Colinsella*) and Proteobacteria (Enterobacter spp.). The relative proportions of each of these taxa vary dramatically not only between individuals, but even within a single individual throughout his lifetime (Fig. 1) [12–16].

Besides the major types such as *Actinobacteria, Bacteroidetes, Firmicutes*, and *Proteobacteria*, the adult intestinal metabolome encompasses members of less diverse bacterial types, including *Verrucomicrobia, Lentisphaerae, Synergistetes, Planctomycetes, Tenericutes,* and *Deinococcus-Thermus*. In addition to these established phylogenetic groups, SSU rRNA gene sequences of uncultured bacteria can be detected. They cluster within the candidate types TM7, *Melainabacteria* and *Gemmatimonacetes*.

Although each individual's microbiome is unique, studies of taxonomic units and microbiomes in different countries have revealed several common microbial communities [2, 13].

At the same time, the composition of Western microbiomes differed from non-Western microbiomes in a number of parameters [17–26]. First of all, the first ones have 15–30% less microbial species than the second ones [18, 22, 23]. Furthermore,

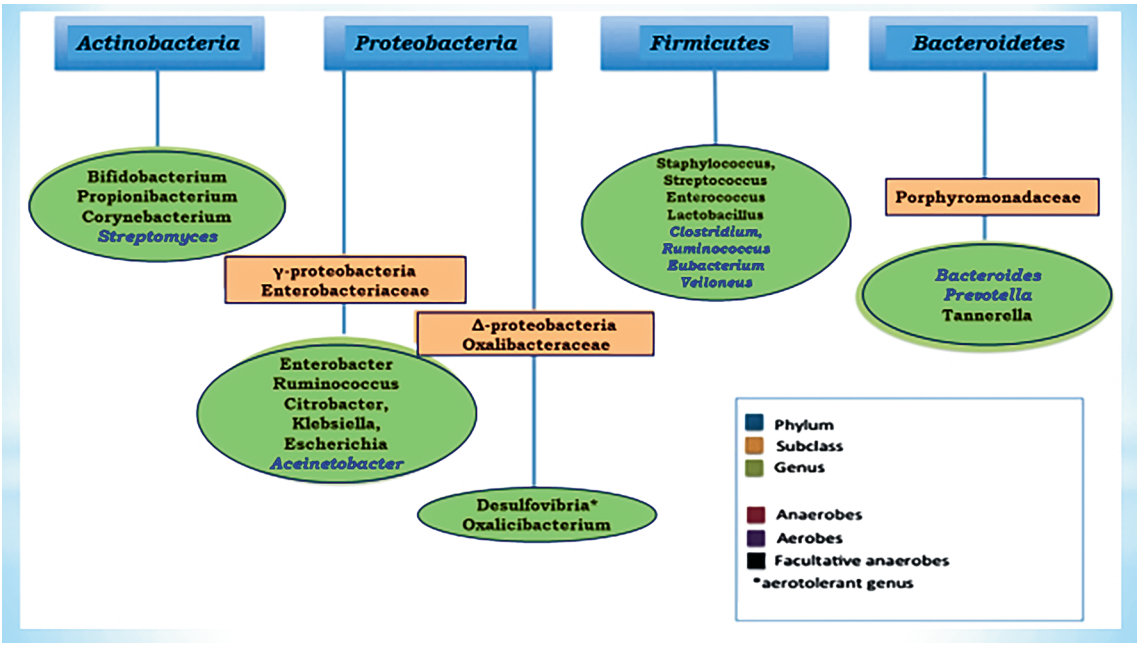

Fig. 1. Major taxonomic units of the human intestinal microbiome

Рис. 1. Крупнейшие таксономические единицы кишечного микробиома человека

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western microbiomes lack certain species that are consistently found in non-western samples. For instance, spiral bacteria of the genus *Treponema*, which appear in the feces of numerous non-Western populations that use raw and wild foods (hunting, fishing, mushroom and berry picking, etc.) [17, 19, 23]. The relative abundance of common types also differs between western and non-western microbiomes. Western ones tend to contain more Bacteroides, whereas non-Western ones contain *Firmicutes* and *Proteobacteria* [19, 21], although there are exceptions to this trend [17].

Thus, studies point to the fact that there is no single "human microbiome" but rather a wide range of configurations that our commensal microbiomes take on.

The existence of these differences in human populations is attributed to diversity in culture, habitat, level of urbanization, hygiene, medicine, lifestyle and diet.

It has been observed that the shift in human diet toward meat-eating over evolutionary time scales is accompanied by a transformation of the intestinal microbial communities [27, 28]. At the same time, increasing fiber and reducing sugar, fat, and meat, a non-Western diet, promotes gut bacterial enrichment [17, 29–31]. Some of the same genes and signaling pathways that differ in quantity between herbivore and carnivore microbiomes also shift rapidly in humans who switch from a vegetarian to an omnivorous diet [30].

One of the hypotheses for the decline in species diversity of the microbiome states that technological and cultural changes accompanying industrialization lead to a "vanishing microbiome" [32]. In addition, living in urban environments, contact with animals, overuse of antibiotics at an early age [32–34], all sorts of intestinal parasites in Western populations [24, 35, 36], and physiological variations such as human-specific loss of N-glycolylneuraminic acid (Neu5Gc) make some contributions.

Alternatively, parts of the microbiome may simply diverge along with human populations as the latter move around the world. For example, the current distribution of *Helicobacter pylori* strains coincides with known human migrations [14, 37].

DEVELOPMENT OF THE GUT MICROBIOME IN ONTOGENESIS

The results of metagenomic studies of the genetic composition and metabolic profile of the intestinal microbiota indicate that this microbiome represents a separate extracorporeal organ of the human body [38]. Like any system (organ) of the organism, the gut microbiome undergoes certain stages of development and maturation.

Intestinal colonization in healthy children fits into four consecutive temporal phases:

- The first lasts from birth to two weeks;
- the second begins after two weeks and lasts until the introduction of the first complementary food;
- The third phase lasts from the introduction of the first complementary food until the end of breastfeeding;
- the fourth — after the cessation of breastfeeding.

From the modern point of view, it is still more correct to distinguish five time intervals, including the antenatal period, and if we consider the entire life course of an individual, then six, taking into account the elderly and old age.

According to many scientists, the intrauterine and neonatal periods are critical stages in the formation of the child's microbiome, which largely determines the state of his or her health throughout life [39, 40].

FROM FERTILIZATION TO BIRTH

Until recently, it was believed that the fetus in the womb is completely shielded from contact with the microcosm, meaning that its antenatal development takes place in an aseptic environment, and the contamination process is established at birth.

A scientific search uses a combination of technologies, namely bacterial DNA sequencing, fluorescence *in situ* hybridization (FISH) method and bacterial culturing in order to determine the presence and viability of the fetal microbiome. It indicates that microbial colonization begins long before birth and is directly dependent on the microecology of the mother [41]. Bacteria of the genera *Enterococcus, Escherichia, Leuconostoc, Lactococcus* and *Streptococcus* are present in the placenta, amniotic fluid, cord blood and meconium [42–52]. Spanish researchers found DNA from bacteria of the genera *Lactobacillus* and *Escherichia coli* in primary stool samples of 20 newborns [43].

In 2014, researchers in Houston, Texas, identified genetic sequences of bacteria from the placentas of 320 women. Biological material was collected immediately after delivery from the germinal part of the placenta (chorionic villi), i.e. the selected samples were not in contact with the microbiota of the birth canal. A wide range of microorganisms were identified in the tissues examined, indicating the existence of a unique placental microbiome. This suggests that the first encounters

with microbes in the infant occur prenatally, even in healthy pregnancies, and are of great importance for both fetal development and the subsequent establishment of the child's microbial system [47].

One study obtained evidence of intrauterine penetration of bacteria from the gut of the mother to the fetus [51]. The researchers assumed that this occurs via the bloodstream and/or lymphatics, a mechanism similar to the "gut-breast axis". This hypothesis is supported by the data of another experiment in which pregnant mice orally received labeled *Enterococcus faecium*, after which these bacteria were detected in the placenta and even in the meconium of unborn mice [51].

A study led by C. Patrick (2019), involved a comprehensive selection of clinical (mother-child) and experimental (female mouse-calf) biomaterial, visualization of the embryonic microbiota in mice, demonstration of dynamic changes in the microbiota during pregnancy in both maternal and fetal (embryonic) sites, and evaluation of the viability of cultured components. Data from the mouse model clearly show that the mouse fetus is exposed to viable and culturable bacteria only in mid-pregnancy, despite positive sequencing results that demonstrate the presence of microorganisms at the end of pregnancy. The authors hypothesized that changes in immune regulation at the level of the utero-fetal barrier may modulate the ability of microorganisms to penetrate and remain viable in the fetal environment.

Clinical results are less clear-cut because the low bacterial biomass of the intrauterine environment (amniotic sac with fetus and germinal part of the placenta) makes it difficult to isolate "contaminants" (bacteria) that may be introduced during sample collection and preparation. However, bacterial signatures that could not be attributed to laboratory contamination were identified in placentas retrieved during cesarean section surgery using NGS sequencing of total DNA banks. These taxa included *Lactobacillus* DNA. In addition, sequencing and culturing results identified common microbial signatures in individual mother-child dyads and discrepancies between fetal/intrauterine samples and controls. Tracing the source of microbial translocation in both a mouse model and in humans found that the placenta represents the matrix (meaning reservoir) of the microbiota [53].

Despite the vast amount of experimental studies, antenatal colonization of the infant remains an area of intense study and debate [54].

Recent developments in a large cohort of women have shown that the majority of bacterial DNA sequences identified in the terminal villi of the human placenta can be attributed to contamination of the internal environment [55].

In June 2021, K.M. Kennedy et al. concluded with a high degree of evidence that fetal meconium samples do not have a "microbial signal.

The researchers established that intestinal colonization in healthy preterm infants does not occur before birth, and the presence of microbial profiles in neonatal meconium reflects populations acquired during and after birth [56].

The concept of sterile fetal development also remains relevant since the current level of knowledge about the mechanisms and functions of transplacental transfer of free nucleic acids is insufficient.

It is well known that the gut and vaginal microbiome changes during pregnancy, but it is still unknown whether these changes have adaptive significance for the mother and/or child.

Due to changes in vaginal pH during pregnancy, bacterial diversity decreases but stability of the microbiota composition increases. Generally, during this period, the vaginal microbiome is dominated by *Lactobacillus crispatus* and *Lactobacillus iners*. The quantitative predominance of these species emphasizes their importance in carrying a healthy baby and maintaining a healthy birth canal environment. It is believed that an altered maternal microbiome allows the fetus to obtain energy from mother's blood more efficiently or that butyrate-producing bacteria may support intestinal epithelial function and contribute to immune tolerance and nurturing of the unborn child [57–59].

An unfavorable variant of vaginal dysbiosis in pregnant women is a decrease in *Lactobacillus* spp., an increase in *Gardnerella* and *Ureaplasma* spp. and, definitely, a colonization of *Candida albicans*. *Burkholderia, Streptosporangium* and *Anaeromyxobacter bacteria* were found in the placenta of women with preterm labor, while *Paenibacillus* predominated in mature infants [60].

Thus, the type and number of bacteria in the different microbiocenoses and amniotic fluid of the expectant mother are important for the outcome of pregnancy and the birth of a healthy infant.

WHAT WE KNOW

Fertilization takes place in an immune-protected organ, the uterus. In turn, immune protection means lack of colonization, but not infertility specifically. It is possible that some bacterial cells from the cervix [108] penetrate with the sperm during fertilization and reach the egg, accompanying the

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implantation process and the period of early embryonic development. Despite this fact, immunity seems to prevent the establishment of a microbial community in "protected" organs. The uterus, placenta, fetus, and blood appear to be free from microbiota, although they may contain bacterial DNA or even some isolated live bacteria [9].

There is an ongoing debate whether the presence of bacterial DNA contradicts the concept of sterility. It has been shown that the presence of circulating bacterial DNA in the blood or placenta, or even the sporadic finding of live transient bacteria, does not indicate infection and does not challenge the current paradigm of immune-mediated organ sterility [47, 61]. Of course, transient "minisepsis" can occur when live microbial cells enter the blood after trauma, microtrauma, or "leakage" of mucous membranes (rupture of fetal membranes or formation of microscopic fissures in them) [62]. In addition, transient bacteremia due to tooth brushing in individuals with periodontal disease is possible [63]. Foreign elements will undergo elimination by phagocytic cells in healthy individuals with an adequate immune response sooner than colonization and assembly of microbial communities occurs. Otherwise, if it concerns a future mother, a complicated course of pregnancy is possible.

K. Aagaard et al. (2014) compared the taxonomic profile of the microbiome of the placenta and various microbiocenoses (intestine, oral cavity, skin, genitourinary tract) of a pregnant woman, and found the maximum similarity of the microbiome composition between the placenta and oral cavity. Representatives of *Proteobacteria* predominate in the placental microbiome. Such species as *Prevotella tannerae* and *Neisseria* are also frequently detected [47].

The similarity in the composition of the oral and placental microbiome implies, as mentioned earlier, the translocation of oral bacteria into the placenta. This may explain the fact that odontogenic (periodontitis) and tonsilogenic maternal infections increase the risk of preterm labor, pregnancy and delivery complications [64, 65]. The presence of certain bacteria within the oral microbiota (e.g. *Actinomyces naselundii*) is associated with lower birth weight and preterm labor, while the presence of lactobacilli is associated with higher birth weight and later labor [66].

MODE OF DELIVERY AND THE GUT MICROBIOME OF THE NEWBORN

Pregnancy and labor present the first major exposure of the complex maternal microbiota to an infant and ensure intergenerational transmission of the microbiome. Rupture of a chorioamniotic membrane makes possible contact of an infant with mother's vaginal and perineal microbes. It is no coincidence that prolonged labor poses a risk of infection of an infant with opportunistic microbiota [67].

Mature infants born naturally (vaginally) ingest representatives of the mother's vaginal and intestinal microbiota in small amounts. These are mainly bacteria of the genera *Prevotella, Sneathia* and *Lactobacillus*, belonging to the phylum *Firmicutes*, class *Bacilli* of the genus *Propionibacterium* (phylum *Actinobacteria*, class *Actinobacteria*) and family *Enterobacteriaceae* (phylum *Proteobacteria*, class *Gammaproteobacteria*) [68].

In other words, the gastrointestinal tract of a newborn is intensively populated by aerobic and facultative anaerobic bacteria, which, on the one hand, reduce the oxygen concentration in the intestine and prepare conditions for colonization by obligate anaerobes, and, on the other hand, show proinflammatory potential, which is accompanied by the development of mild intestinal inflammation and the presence of mucus in the transient stool of an infant. Abundant contamination of the newborn's bioniche with *Lactobacillus* spp., the main representatives of the vaginal microbiome, establishes protection against pathogenic and opportunistic microorganisms, as well as provides maximum compatibility with the subsequent intake of lactobacilli from breast milk.

From the end of the first week of life, the intestinal microbiome of an infant undergoes a transformation: the level of strict anaerobes such as *Bifidobacterium* (phylum *Actinobacteria*), *Bacteroidia* (phylum *Bacteroidetes*) and *Clostridia* (phylum *Firmicutes*) begins to dominate, leading to the suppression of aerobic bacteria and, to some extent, facultative anaerobes such as *Propionibacterium* and *Enterobacteriaceae*. Since then, the intestinal microbiota becomes very similar to the intestinal microbiota of a one-month-old infant if the infant receives breast milk [69–71].

The intestinal microbiota of the mother is generally considered to be the source of *Bifidobacterium* and *Bacteroidia* for the child. Thus, we inherit the primary microbiota from our mothers, grandmothers and further down the maternal line [72]. By the second year of life, the child's microbiota resembles the adult one [68].

There is accumulating evidence that the human gut ecosystem is critical in the establishment and maturation of immunobiologic reactivity [73]. The presence of fetal microorganisms and/or their molecular signatures stimulates the fetal mucosal

immune response and prepares fetal tissues for colonization after birth [74, 75].

A recent study demonstrated the presence of tissue-resident memory cell-like T cells in the human fetal intestine, which, when stimulated, secrete more proinflammatory cytokines than naive T cells [76]. These results suggest that the fetal intestine is exposed to foreign antigens, but it is still unknown whether these antigens are microbial.

Thus, the intestinal colonization pattern which has been established during the first week of life is ulteriorly reflected in the microbial community of the human intestinal microbiome through various factors (genetics, diet, environment, lifestyle, etc.) [77–80].

THE INFANT'S FEEDING PATTERN AND THE MICROBIOME

As mentioned above, mother's microbiome and the sanitary state of environment determine the nature of the primary colonization. Subsequently, the composition of the intestinal microbiota largely depends on the type of feeding.

Breast milk (BM) is the first optimally balanced product with a complex biochemical composition, received by the infant almost immediately after birth. BM remains the only nutritional substrate for the first 4–6 months.

BM protects an infant from infectious diseases during the first days of life and contributes to the reduction of mortality due to the presence of many specific and nonspecific defense components: T- and B-lymphocytes, plasma cells, immunoglobulins (primarily IgA) and antimicrobial enzymes (lysozyme and lactoferrin) [81].

It has been established that breastfeeding prevents chronic diseases such as diabetes mellitus [82], obesity, hypercholesterolemia [83]. Undoubtedly, BM serves as a significant factor in the formation of a "healthy" microbiome of the child, since it is the main source of symbiotic microorganisms (bifidobacteria, lactobacilli, enterococci). BM also contains substances with antimicrobial and prebiotic potential: β-lactose, α-lactalbumin, lactoferrin, oligosaccharides, nucleotides, nucleosides, sIgA, leukocytes, lysozyme, and others. [84–86].

Low levels of phosphorus, β-lactose, and short-chain fatty acids (SCFAs) reduce the pH of the intestinal environment, inhibiting the proliferative growth of opportunistic and pathogenic bacteria and providing an optimal titer of resident (obligate) BM microbiota (at least 10^3 CFU/mL of live bacteria and a wide range of bacterial DNA) [87].

There is no doubt that the intestinal microbiota of an exclusively breastfed child is characterized by a high level of bifidobacteria (90%) and low levels of *C. difficile* and *E. coli* [79]. However, it should be emphasized that for the first three days of the baby's life adult strains (*B. longum* and *B. catenulatum*) dominate the structure of bifidobacteria. However, they are substituted by infant strains (*B. infantis* and *B. breve*) by the second week under favorable conditions [88]. Studies conducted at the genetic and molecular level have established that the genome of infant bifidobacterial species contains 5 genes that encode the synthesis of bacterial galactosidases. For example, *B. infantis* produces the enzyme *β-galactosidases* and *B. breve* produces endogalactanase, which enable bifidobacteria to metabolize oligosaccharides contained in breast milk (BM) [89–91].

The dominance of infant strains of bifidobacteria contributes to the formation of immunologic tolerance, reduction of inflammation activity, and strengthening of the intestinal protective barrier. The above mentioned is illustrated by the work of Y.M. Sjögren et al. (2009). It was noted that by the end of the newborn period there was a direct correlation between the level of sIgA in intestinal secretion and the number of bifidobacteria, and an inverse correlation between the level of proinflammatory cytokine IL-6 and *Bacteroides* [92].

Nowadays, more than 400 different bacterial species, including staphylococci, lactic acid bacteria and bifidobacteria, have been isolated from BM samples. However, the cultured bacterial diversity detected in individual samples is much lower (2 to 8 different species per woman). Similar microbial species have been identified in the feces of infants, confirming the role of BM in bacterial colonization of the gut [93].

In general, the BM microbiome is quite complex. The identification of bacterial species using culture and molecular methods has identified cutaneous and gut-associated microorganisms such as *Staphylococcus, Streptococcus, Escherichia, Enterococcus, Veillonella, Prevotella, Pseudomonas* and *Clostridia* [94–99]. In addition, its dynamism and variability throughout lactation has been identified. Thus, the colostrum contains a large diversity of typical skin and intestinal-type microorganisms, whereas the microbiota in mature milk is less diverse and is represented by a significant number of infant oral bacteria and skin [100].

It is well known that the composition of the BM microbiome is modified by maternal factors: maternal somatic health, mode of delivery, stress, body mass index (BMI), antibiotic use, diet and place of residence [18, 29].

Leyva L. Lopez et al. (2021, 2022) evaluated the variability of the BM microbiota according to maternal age, BMI, stage of lactation, subclinical mastitis (SCM) and breastfeeding practices: exclusively breastfed, predominantly breastfed or mixed feeding. Breast milk samples (n=86) were studied by 16S rRNA sequencing. According to the results of molecular genetic analysis, the most numerous genus inhabiting BM was Streptococcus — 33.8%, almost 2–3 times less frequently isolated Pseudomonas — 18.7% and Sphingobium — 10.7%. The relative abundance of the represented genera correlated with maternal factors [101, 102].

First, *Lactobacillus, Streptococcus* (phyla *Firmicutes*) and bacteria of phyla *Actinobacteria* were significantly more prevalent in early lactation, whereas oral *Leptotrichia* (phyla *Bacteroidetes*) and environmental *Comamonas* (phyla *Pseudomonadota*) were more prevalent in established lactation.

Second, intense proliferative growth of *Streptococcus, Lactobacillus, Lactococcus, Lactococcus, Leuconostoc* and *Micrococcus* was observed in multiparous women compared to primaparous ones.

Third, a diverse microbiota characterized by higher levels of lactic acid bacteria (*Lactobacillus*, *Leuconostoc* and *Lactococcus*), *Leucobacter* and *Micrococcus* was found in mothers with optimal BMI (19–25) compared to mothers with altered BMI [101]. In addition, individual microbial communities differed according to the stage of lactation and feeding method. More differentiated microbial species were detected in BM samples of women who performed exclusive breast feeding during all periods of lactation, compared to BM samples of women who supplemented their infants (11 vs. 1 and 13 vs. 2, respectively). In addition, the former were significantly more likely to have commensal and lactic acid bacteria, including *Lactobacillus gasseri, Granulicatella elegans, Streptococcus mitis* and *Streptococcus* parasanguinis, compared to the latter at the beginning and end of lactation.

Thus, the addition of herbal teas and/or complementary foods to the infant's diet leads to a transformation of the BM microbiome as a result of decreasing the number of bacteria which contaminate breast milk from the infant's oral cavity and increasing the "environmentally friendly" bacteria which migrate into breast milk from the mother's intestine [102].

The study performed in China examined the variability of the BM microbiome according to the duration of lactation, age, maternal residence and the presence of gestational arterial hypertension syndrome (gestational AH) in different areas of China. The researchers found the highest microbial diversity in the colostrum, which gradually decreases and changes throughout lactation. Thus, at the phyla level, the numbers of *Proteobacteria* increased and *Firmicutes* showed the opposite trend; at the genus level, *Staphylococcus, Streptococcus, Acinetobacter, Pseudomonas* and *Lactobacillus* dominated in the milk samples and expressed certain variations during lactation. The geographical location of the mother significantly influenced the formation of the BM microbiota and the number of the predominant genus. In addition, milk from healthy mothers had more diverse microbial community at the genus level during early lactation than milk from mothers with gestational arterial hypertension [103].

Since BM microbiota is involved in the formation of infant's intestinal microbiome through initial GIT inoculation, it has been assigned a status — "Mother Nature's prototype probiotic food" [154]. Infants exclusively breastfed for the first 3–4 months of life, consuming about 800 ml of GM per day, receive ~10^5–10^7 CFU of bacteria from milk, which certainly determines the main species composition of the gut microbiome.

A cross-adoption experiment showed that it is the breastfeeding mother, not the biological one, who determines the composition of the infant's microbiome, which persists after weaning and over a lifetime [104]. As part of the Human Microbiome Project, T. Ding and P.D. Schloss (2014) further confirmed that breastfeeding in infancy is a major life cycle characteristic that influences bacterial composition in adults [105].

Non-exclusive models have been proposed to collect BM samples (Fig. 2).

1. *Transfer of microorganisms from maternal skin to breast milk.* Molecular approaches have been used for genetic typing of Gram-positive organisms contaminating both maternal and infant skin as well as breast milk in order to demonstrate the association of specific strains in the dyad [106, 107]. The nipple and areola are in the infant's oral cavity, resulting in the introduction of maternal skin-associated bacteria into the infant's mouth and gastrointestinal (GI) tract during breastfeeding [108].

2. *Retrograde flow of microorganisms from the infant's mouth to the mammary ducts* [97]. Based on the physiology of infant suckling, it is possible that there is a retrograde flow of breast milk from the infant's mouth through the nipple into the mammary gland [109, 110]. This mechanism explains the presence of *Gemella, Veillonella, Staphylococcus,* and *Streptococcus* microorganisms in both the in-

fants' oral cavity and breast milk [97, 111]. Other bacteria such as Actinomyces were not always detected in BM although they commonly inhabit the oral cavity of newborns. In addition, DNA signatures of bacteria were detected in initial samples of colostrum even before breastfeeding has started [98]. Thus, although milk transfer from the infant's oral cavity can explain the presence of some microbes, it cannot fully reveal the composition of the BM microbiota.

3. *An alternative model to explain the presence of typical intestinal microorganisms in the BM.* Dendritic cells (DCs) of the intestinal mucosa regularly ingest intestinal bacteria and transport them to local lymphoid follicles, where specific IgA is produced. DCs and immunoglobulin-secreting lymphocytes circulate in the blood but can selectively return to the intestine through interaction with β7-integrins and adhesion molecules secreted by endotheliocytes (adressins, MAdCAM-1). Mammary gland endothelial cells synthesize MAdCAM-1 molecules during pregnancy, allowing selective entry of "programmed" DCs containing gut bacteria into the gland. These microorganisms or their DNA, as well as DNA from other microorganisms, can directly enter the infant GIT and alter the structure of microbial communities, providing the basis for the *entero-mammalian tract* (EMT) model.

The EMT model is supported by three studies involving the mother and the preterm infant. A subset of genomic signatures corresponding to *Bifidobacterium longum, Streptococcus thermophilus* and *Bifidobacterium* pseudocatenulatum appeared to be shared by maternal stool, maternal blood, breast milk and infant stool samples [91, 106, 112]. Several studies also emphasize that some bacteria presented in the mother's gut are able to reach her mammary gland not only during lactation but also in late pregnancy through a mechanism involving intestinal dendritic cells and macrophages [113].

4. *Mechanism of microbiota transmission from mothers to breast milk by spreading from the mammary gland.* Experiments in a mouse model of cytomegalovirus (CMV, CMV) have demonstrated that viruses can remain dormant in the mammary gland after primary infection [114]. It is hypothesized that the process of lactation reactivates these viruses. In accordance with this idea, CMV has been detected in the BM of asymptomatic CMV seropositive women. Virolactia, the presence of live virus in the BM, correlates with the duration of lactation and peaks in the 3–4th week of lactation. It has been noted that CMV excretion was

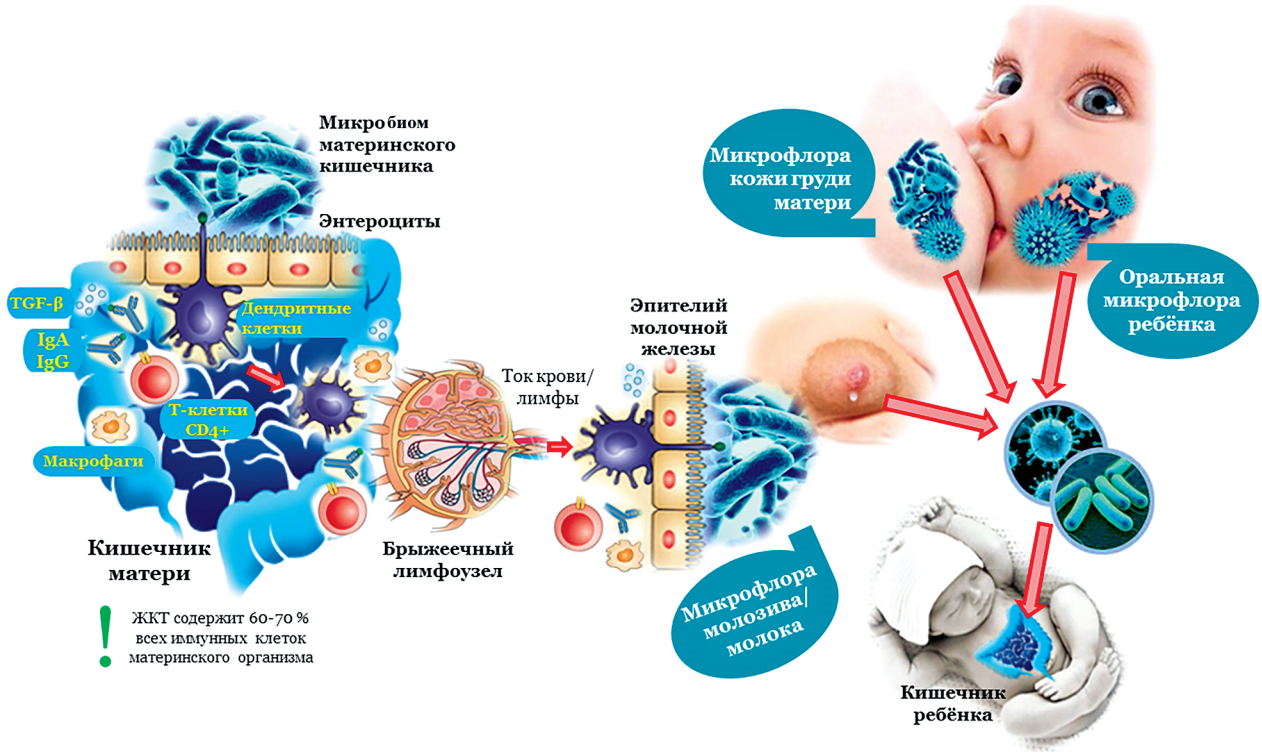

Fig. 2. Models of breast milk microbiome assembly (Source: Latuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. Semin Reprod Med. 2014 Jan;32(1):68-73)

Рис. 2. Модели сборки микробиома грудного молока (Источник: Latuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. Semin Reprod Med. 2014 Jan;32(1):68–73)

apparently restricted to breast milk [115]. Preterm infants may be at risk of postnatal CMV infection through breast milk as a result of reduced transplacental transmission of CMV antibodies [116]. Clinical evidence supports the fact that CMV excretion in mothers of preterm infants may depend on local immune factors in the mammary gland [117].

COMPLEMENTARY FOOD INTRODUCTION AND THE GUT MICROBIOME OF THE INFANT

The gradual introduction of complementary foods (CF) modifies the bacterial diversity in the infant gut. It has been noted that the gut microbiota becomes more complex since proliferative growth of bacteroidetes and other representatives of anaerobic microbiota is induced. Subsequently, the total number of bifidobacteria is suppressed and the species affiliation is transformed: infant species are being replaced by adult species such as *B. longum, B. adolescentis, and B. catenulatum* [118–122].

Along with genetically encoded nutritional factors, these changes in the gut microbiota determine gut ontogeny at the beginning of solid food intake [123]. For example, experiments in sterile mice have shown that bacterial colonization of the gut is required for the regulation of weaning-induced antimicrobial peptide expression [124]. In addition,this transition from breastfeeding to contemporary food promotes the formation of the intestinal barrier and induces profound intestinal remodeling [125–129].

Complementary foods introduce new substrates. Their assimilation requires bacterial populations with appropriate metabolic activity, which begins to remodel when solid food is introduced. It continues at least until the age of 3 years, microbial diversity parallelly increases [130].

Dietary enlargement is also accompanied by a restructuring of the immune status. An experimental work conducted on rats showed that weaning of suckers induced αβ-TCR(+) T cells in the lymphoid tissue associated with the intestine. Moreover, receptors to IL-2 were increased, these receptors may contribute to the development of allergic inflammation [131].

Bacterial hydrolysis products, primarily short-chain fatty acids (SCFAs), are known to play a modulatory role in metabolism and immunity in the child. Butyrate is an energy source for colonocytes. It maintains the integrity of the epithelium in the intestine [132]. In addition, it promotes Treg cell differentiation and suppresses inflammatory responses as shown in bacterial butyrate producers such as *Faecalibacterium prausnitzii* [130, 133, 134]. Propionate also potentiates *de novo* Treg cell formation in the periphery [133].

An experiment on suckling rabbits identified 29 metabolites. It revealed a strong modification of the cecal metabolome after the initiation of solid food intake. Thus, the concentration of short-chained fatty acids, the main bacterial metabolites, increased: 10-fold for butyrate, 5-fold for acetate and 2-fold for propionate. In addition, high concentrations of methanol and two sugars (glucose and ribose) were detected in cecum. The predicted relative number of microbial pathways involved in the production of propionate, acetate and butyrate increased.

Taking into account these results, the scientists suggested that changes in the cecal metabolome may be a signal which triggers the maturation of the epithelial intestinal barrier. The regulatory function of the blind intestinal mucosal transcriptome was assessed to confirm hypothesis presented.

In vitro metabolomic and transcriptomic analyses have demonstrated that the change in microbiota composition at the beginning of solid food intake is associated with a major shift in the production of bacterial metabolites that coincides with transcriptomic regulation of key components of both the immune and physical intestinal barrier. Metabolites of the intestinal microbiota, namely butyrate [135], partly induce the maturation of the intestinal barrier during weaning.

When the volume of BM is significantly less than solid food, the end of breastfeeding is accompanied by relative stability of microbial composition [136]. This period is notable for the appearance of adult intestinal bacteria representatives of *Bacteroidetes, Firmicutes* types and the *Clostridia class: Clostridium, Ruminococcus, Faecalibacterium, Roseburia* and *Anaerostipes* [118, 137].

Thus, microbial composition is usually highly unstable and lacks species diversity during the first year of life [138–140]. Nevertheless, a number of studies have shown that some bacteria which are common for adult microbiome colonize infants' GIT from the first months of life [106, 141].

ENVIRONMENTAL FACTORS AND THE GUT MICROBIOME OF THE INFANT

In the last decade it has been proven that the composition of intestinal microbiota is significantly influenced by the residence. It is explained by differences in the environmental situation, nutrition, lifestyle and traditions existing in a certain territory.

M. Fallani et al. (2010) conducted a multicenter study of the intestinal microbiome in infants from five European countries: Sweden, Scotland, Germany, Italy and Spain. The place of residence, mode of delivery, dietary patterns, and antibiotic use were studied for the fecal microbiota composition. Infants aged 6 weeks (n=606) were included into the study. It was established that the area of residence influenced the intestinal microbiota of infants as much as the mode of delivery or feeding did [142].

The researchers noted that children living in the north of Europe had higher levels of *Bifidobacteria*, *Atopobium, C. perfringens,* and *C. difficile*, while southern infants had higher levels of *Bacteroides, Eubacteria,* and *Lactobacillus*. Researchers concluded that differences in diet and lifestyle in different European countries may affect the formation of the child's intestinal microbiome [142].

Children born in poor areas of developing countries are exposed to microbial colonization earlier than infants in rich and highly developed societies. Thus, as there is no competition among bacteria of the genus *Enterobacter*, newborns living in high economic countries tend to be colonized by "skin bacteria" — *Staphylococcus epidermidis* [143]. This reformed colonization process, associated with increased hygiene measures, may have an irreparable impact on the development of both the overall microbiome and the immune system of infants.

The probability of sharing bacteria through household items and indoor air is shown to increase commensurately with the number of people living in a house. S.J. Song et al. (2013) found that members of the same family living together in a limited area have more similar microbiomes than relatives living separately [144]. The maximal relatedness of the skin microbiome among spouses is particularly indicative, as well as the sharing of surface bacterial communities between hosts and their dogs [92].

Such factors as prolonged living of a future mother in countryside, frequent contact of an infant with domestic animals and, consequently, with their microbiota in the first year of life, have a protective effect, increasing immunologic tolerance [145, 146]. Thus, growing up in a more diverse microbial ecosystem helps train a child's immune system not to overreact to triggers, and reduces the likelihood of asthma, allergies, and inflammatory bowel disease (IBD) [147–149].

Kindergarten is another external factor that contributes to the maturation and formation of the intestinal microbiome at an early age.

Three published studies have examined the relationship between kindergarten daycare and children's GIT microbiota [150–152]. The first study (Thompson A.L., 2015) indicated an increase in α diversity in children visiting kindergarten. The second (Hermes G.D.A., 2020) failed to demonstrate a significant contribution of attending a kindergarten in shaping the microbiome. The third (Mortensen M.S., 2018) — examined interindividual (β-diversity) and intraindividual (α-diversity) variability in microbiota, antibiotic and disease resistance in children aged 1–6 years.

The studies conducted had a completely different design, lacking: a comparison group (participants of appropriate age who did not attend kindergarten) and consideration of additional factors that significantly adjust the structure of the microbiome. As a result, completely different data were obtained, which did not allow us to conclude: whether a child's prolonged presence in kindergarten has an impact on the character of the intestinal microbiota and if there is the significance of this impact.

The tremendous work carried out under the guidance of A. Amir (2022) made a significant contribution to identify differences in the composition of the gut microbial ecosystem in organized and unorganized children. The researchers took into account all the shortcomings of previous experiments and expanded the list of additional factors. The study included children of different ages from four kindergartens, and a comparison group — children of the same age, but brought up at home. The material for analysis covered four time intervals and took into account the age of the child at the time of entering kindergarten and the length of time in an organized group. Overall, the cohorts did not differ significantly in demographic and test characteristics.

The longitudinal nature of the cohort of children made it possible to characterize the dynamics of gut microbial composition in organized young children as a small ecosystem. It is emphasized that, microbiome formation is much more influenced by the child's presence in a particular group than by the method of delivery and the nature of feeding, which are leading factors in the first year of life. The research shows that age is the dominant distorting factor in microbial composition not only in the first, but also in the second and third years of life. Other factors showing a modest, but significant contribution were the sex, the time of entry into kindergarten and the duration of attendance, as well as the mother's or child's receipt of antibiotics (both during and within 3 days after delivery),

the nature of feeding, and the age of introduction of solid food (the first complementary food).

It is proved that microbial composition of children attending kindergarten and non-organized (home) children differs. Enrichment of taxa is more often observed in children who visit the same kindergarten for a long period of time without changing the socializing group, compared to children of the same age who have not yet started attending a kindergarten. Taxa from the families *Bifidobacteriaceae* (q=0.04) *Actinobacteria type, Lactobacillaceae* (q=0.05) and *Staphylococcaceae* (q=0.05) of the *Firmicutes* type and *Pasteurellaceae* (q=0.04) of the Proteobacteria family type were significantly more frequently detected in children staying at home. Children visiting kindergaten had increased abundance of the family *Prevotellaceae* and genus *Prevotella* of the *Bacteroidetes* type (q=0.04), as well as *Lachnospiraceae* (q=0.05) and *Ruminococcaceae* (q=0.04) of the *Firmicutes* type.

In addition, the researchers confirmed once again that children of the same age from the same kindergarten are significantly more similar in their microbial landscape than children of the same age from two different kindergartens. Moreover, starting from the second month of attendance, children from the same kindergarten become more similar in their microbial composition. This means that a particular kindergarten contributes to the formation of a collective microbial pattern.

It was interesting to find that the frequency of early kindergarten attendance and the mix of children in the population had an inverse relationship with childhood diabetes. In turn, higher number of children in the group was positively associated with greater protection against diabetes. These data suggest that early exposure may play a role in the development of immunoregulatory mechanisms that protect against diabetes. However, further longitudinal studies are needed to investigate whether the patterns of gut microbial maturation and kindergarten attendance in healthy children are associated with future health and disease, as well as immunologic and allergic outcomes [153].

Thus, the gut microbiome is predominantly shaped by environmental factors, while genetics explains less than 10% of the variation. The first 3 years of life (early childhood) show the highest intra- and interindividual variability in the gut microbiome. It is no coincidence that this time is considered a "critical period" for the maturation of the gut microbiome.

Visiting organized groups is important for the formation of microbial composition in early childhood. A specific child care institution influences the gut microbiome, and the microcosm of each child acquires similar characteristics when regularly attending a child care center. In addition, the gut microbial composition of organized children differs from that of home-raised children. At the same time, enrichment of taxa is more often observed in children who stay in the same child care institution for a long time.

CONCLUSION

Thus, the data of the literature indicate that the formation of intestinal microflora of a child begins from the intrauterine stage and is a long, complex multifactorial process, the violation of which is associated with the development of various pathological conditions in children. A deeper understanding of the mechanism of intestinal microbiota formation in children will make it possible to develop effective methods of prevention and correction of microecological disorders in children and related diseases in different periods of life.

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GUT MICROBIOTA AND PANCREATIC DISEASES

© Marina Yu. Komissarova

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Marina Yu. Komissarova — PhD, Senior Researcher at the Laboratory of Medical and Social Problems in Pediatrics of the National Medical Research Center, Deputy Chief Doctor for Hospitalization of the Clinic. E-mail: komissarova_m_u@mail.ru
ORCID: 0000-0002-1533-4498

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Abstract. This review presents scientific data on the features and mechanisms of the formation of gut microbiota in various pancreatic diseases, as well as factors affecting chronic inflammatory processes.

Key words: *gut microbiota; pancreatic diseases; pancreatitis; diabetes mellitus; metabolic syndrome*

КИШЕЧНАЯ МИКРОБИОТА И ЗАБОЛЕВАНИЯ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Марина Юрьевна Комиссарова — к.м.н., старший научный сотрудник лаборатории медико-социальных проблем в педиатрии НИЦ, заместитель главного врача по госпитализации клиники. E-mail: komissarova_m_u@mail.ru
ORCID: 0000-0002-1533-4498

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Резюме. В обзоре представлены научные данные об особенностях и механизмах формирования кишечной микробиоты при различных заболеваниях поджелудочной железы, а также факторах, влияющих на хронический воспалительный процесс.

Ключевые слова: *кишечная микробиота; заболевания поджелудочной железы; панкреатит; сахарный диабет; метаболический синдром*

The state of the intestinal microbiota significantly affects the onset and development of pancreatic diseases. Studies conducted in experimental conditions and clinical observation confirm the correlation between the gut microbiome and chronic pancreatic inflammation. In addition, the mechanism of chronic inflammation associated with dysbiosis may have a complex effect in causing such conditions as pancreatitis, metabolic syndrome, type 2 diabetes mellitus, and pancreatic tumors. Changes in gut microbiocenosis can be both primary and secondary, they also may affect an organ that does not have its own microbiota.

CHANGES IN THE MICROBIOTA IN ACUTE, CHRONIC AND AUTOIMMUNE PANCREATITIS

Changes in the intestinal microbiome are possible in acute and chronic pancreatitis [109, 123] and may even represent a complete diagnostic tool [8].

The occurrence of **acute pancreatitis** is associated with an imbalance between pro- and anti-inflammatory cytokines [77, 123]. Experimental models revealed hypersecretion of pro-inflammatory TNF-α, IL-1β, IL-6, IL-17A, CXCL1 and IL-18 with a concomitant decrease in Paneth cell-associated antibacterial peptides such as alpha-defensins and lysozyme [42, 44, 111].

Antimicrobial peptides produced by acinar cells and Paneth cells are necessary for intestinal homeostasis, maintenance of intestinal immunity, and control under microbiome composition [128, 131]. Using a mouse model, Ahuja et al. showed that deletion of the Orai1 Ca^{2+} channel in pancreatic acinar cells (Orai1$^{-/-}$ mice) induces several signs of intestinal inflammation and bacterial overgrowth, leading to bacterial translocation, systemic infection and death [72]. Experimental evidence supports the importance of pancreatic antimicrobial secretion in modulating intestinal/pancreatic homeostasis and the integrity of the intestinal immune system.

As inflammation provokes the damage of tissue, pancreatic acinar cells produce several molecules that may have the function of damage-associated molecular patterns (DAMPs) [39], such as high mobility group protein 1 (HMGB1), heat shock protein 70 (Hsp70), cytosolic protease — caspase 1, nucleotide binding domain (NLRP3), adenosine triphosphate (ATP) and DNA [10, 23, 93]. DAMPs contribute to the activation of Toll-like receptors (TLRs) which cover epithelial cells, immune cells, macrophages and other cells that have recognition function (PRRs) and can identify pathogen-associated molecular patterns (PAMPs) [16]. At least 10 different TLRs have been recognized [1] in humans, as well as polymorphisms in TLR3 and TLR6 genes and the extent of expression of long non-coding RNA. They are associated with the severity of pancreatitis [14, 78] and lead to the activation of specific intracellular signaling pathways as well as produce inflammatory cytokines and chemokines [60], which simultaneously protect the host by promoting regeneration of damaged tissue and mucosal immune response [10].

Pancreatitis can be considered as a unique form of immune-mediated inflammation [122], where damaged acinar cells begin to produce the pro-inflammatory cytokine IL-33, which determines the activation of T-cell subpopulations involved in pancreatic inflammation [58].

In acute pancreatitis, inflammation causes intestinal damage by several concomitant pathogenic mechanisms such as alterations in microcirculation, visceral vasoconstriction, and ischemia [12, 71], which increases intestinal permeability and facilitates the translocation of bacteria and toxins to the pancreas and may lead to fibrosis or necrosis [68]. Bacterial translocation may also be responsible for secondary infections associated with a high risk of death [67, 80].

In addition, acute pancreatitis development is associated with an increase in the number of pathogenic bacteria from the families Enterobacteriaceae and Firmicutes and a decrease in the number of beneficial *Bacteroidetes* and *Lactobacillales* [123]. Serum IL-6 levels directly correlated with the number of Enterobacteriaceae and Enterococci and inversely with the number of Bifidobacterium clusters and Clostridium cluster XI. Furthermore, the degree of changes in the gut microbiota determined the severity of disease progression and the likelihood of systemic complications [99].

Acute pancreatitis is also associated with some populations of commensal bacteria. Their occurrence is related to decreased levels of inflammatory cytokines such as IL-1-beta, TNF-alpha, CXCL1 and IL-18, and inversely correlates with the severity of pancreatitis and systemic infectious complications. From a clinical perspective, restoring the physiologic composition of the gut microbiota may be a useful strategy for the treatment of acute pancreatitis [48, 69, 73, 139]. Qin et al. demonstrated that restoring the physiologic ratio of commensals/pathogens in 76 patients with acute pancreatitis resulted in limiting systemic infectious complications [64]. In a number of other studies, oral administration of probiotics showed no significant effect on the outcome of the disease or prevention of complications [62, 73, 75].

Chronic pancreatitis is the outcome of long-term inflammation leading to chronic damage and dysfunction of the gland [5, 13].

In 30% of patients, chronic pancreatitis is accompanied by a syndrome of bacterial overgrowth, but specific changes in the composition of the microbiota are not fully understood [51–81]. Some authors have observed an increase in *Firmicutes* and a relative decrease in *Bacteroidetes* [109]. Patients with pancreatitis are also affected by progressive and duration-dependent decrease in the commensal bacteria *Faecalibacterium prausnitzii* [28, 109], which promote mucin production and tight junction protein synthesis [65], induce the anti-inflammatory cytokine IL-10 [89], and regulate intestinal T-cell responses indicating a prolonged impairment of mucosal integrity [109]. The level of *Faecalibacterium prausnitzii* was negatively correlated with the level of endotoxins in plasma, its elevation is associated with disorders of carbohydrate metabolism. In addition, patients with chronic pancreatitis have reduced levels of *Ruminococcus bromii* [109], which play an important physiologic role in starch degradation in the colon [133]. Its decrease is associated with disruption of the intestinal mucosal barrier as well as altering glucose metabolism.

Several studies indicate a decrease in *Bacteroidetes* gram-negative bacteria, which are a source of lipopolysaccharides. In fact, lipopolysaccharides may activate the production of pro-inflammatory cytokines associated with NF-κB by binding TLR4 [54]. Patients with chronic pancreatitis have higher levels of lipopolysaccharides and endotoxin which correlate with disease duration and may cause pancreatic beta-cell dysfunction, exacerbating impaired glucose metabolism [2] and involving pancreatic islet cells in the inflammatory process. Chronic pancreatitis results in an increase in both Th1 and Th17 cells [96] which are associated with proinflammatory cytokines such as IFN-γ in pancreatic islets [104].

Autoimmune pancreatitis accounts for approximately 5% of all cases of pancreatitis and is often associated with other autoimmune diseases [55, 110]. One of the diagnostic criteria is elevated serum IgG4 levels [33, 38]. A genetic predisposition to autoimmune pancreatitis has been found [30], but the pathogenesis of the disease remains incompletely understood [121].

Helicobacter pylori is associated with autoimmune pancreatitis [61, 79]. The bacterium triggers immune responses against host tissues because of its molecular similarity [57]. Guarneri et al. reported homology between human carboanhydrase II (CA-II) and *Helicobacter pylori* alpha-carboanhydrase (HpCA). CA-II is a pancreatic epithelial enzyme. Its specific serum antibodies characterize AIP. At the same time, the bacterial homolog segments contain a high-risk HLA-DR allele binding motif. Thus, *Helicobacter pylori* may cause disease in genetically predisposed individuals [36].

Other studies demonstrate the relationship of bacterial infection with the development of autoimmune pancreatitis. In particular, *Escherichia coli* provokes severe pancreatic inflammation with subsequent fibrosis in the mouse model which is similar to the human morphological picture [87]. A number of specific microbial antigens can induce the development of pancreatitis by activating immune responses. Gram-negative bacteria associated with LPS are able to activate the immune response through TLRs [1]. Several TLRs (TLR2, TLR3, TLR4, TLR5 and TLR7) have been affiliated with the development of AIP [10, 119, 120]. Among them, TLR3 usually recognizes microbial ds-RNA that activates FAS/FasL-mediated cytotoxicity that is responsible for chronic inflammation [136]. Finally, TLR7 is capable of recognizing viral ssRNA, thereby activating proinflammatory signaling cascades [91].

MICROBIOTA CHANGES IN TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (type 1 DM) is characterized by loss of insulin secretion due to damage of pancreatic beta cells caused by an autoimmune process against a background of bacterial infection [107].

Several changes in the composition of the intestinal microbiota have been linked to the development of type 1 DM. In a recent study of 76 children at high genetic risk, it was demonstrated that early changes in the composition of the intestinal microbiome predict the onset of type 1 DM [21, 29]. Specifically, *Bacteroidesdorei* and *Bacteroidesvulgatus* are elevated in the microbiome of the type 1 DM predisposed children. In contrast, individuals with late-onset type 1 DM show both similar increase in Bacteroides species and decrease in *Clostridium leptum* [10, 82].

A number of bacterial or viral antigens (Coxsackie A and B viruses, Echo, enterovirus, and others) have been associated with the development of type 1 DM in children and adolescents [27, 115].

Type 1 D is accompanied by profound changes in the composition of the gut microbiota and associated metabolites [25, 100]. Significantly, changes occur in the ratio of butyrate-producing *Bacteroidetes* and *Firmicutes bacteria* [32–66]. The number of butyrate-producing and mucin-degrading bacteria (*Prevotella* and *Akkermansia muciniphila*) decreases [117], while there is an overgrowth of *Klebsiella* bacteria producing short-chain fatty acids (SCFAs).

F. Semenkovich et al. demonstrated bidirectional links between changes in gut microbiota and inflammation associated with type 1 DM. The gut microbiota in the NOD mouse model was able to drive hormonal changes in the testosterone axis (in males) that led to susceptibility to type 1 DM. In turn, hormonal levels were able to alter the microbial landscape in the gut. This phenomenon may be a possible explanation for the different susceptibility between the sexes [25, 31].

There was detected decreased levels of *Lactobacillus* and *Bifidobacterium species*, lymphopenia [108] and upregulation of Th17 cells [52] in a mouse model with type 1 DM [26]. These data support the hypothesis that changes in the composition of the gut microbiota are associated with mucosal immune system abnormalities and that both mechanisms are involved in the pathogenesis of type 1 DM [125]. Increased gut permeability provokes the course of type 1 DM either through beta-cell injury or through bacterial translocation

and associated antigen presentation [94], or directly through beta-cell dysfunction mediated by microbial toxins such as streptozotocin [125].

The effects of diet and drugs have been studied in a similar manner. A study in non-obese diabetic mice showed that exposure to acidified water was able to increase the presence of mucosal and spleen T-regulatory cells (Tregs) and decrease the number of Th17 cells, thereby reducing the likelihood of developing type 1 DM [50]. Modeling in mice has demonstrated that insulin treatment can positively influence the restoration of a healthy gut microbiocenosis [105]. At the same time, oral administration of vancomycin during the newborn period in diabetic mice without obesity reduced the presence of several major genera of Gram-positive and Gram-negative bacteria and resulted in the formation of a single dominant species, *Akkermansia muciniphila* [37].

In addition, innate and acquired mucosal immunity plays a special role in the pathogenesis of type 1 DM. Nucleotide-binding protein 2 containing oligomerization domain (Nod2) has been identified as a susceptibility factor for type 1 DM [137]. Nod2, mainly expressed by neutrophils and monocytes/macrophages, recognizes bacterial molecules that possess the muramyl dipeptide (MDP) fragment and stimulates the immune response by inducing $CD4^+$ Th1 and $CD4^+$ Th17 cells in pancreatic tissue, promoting autoantibody production and tissue damage [102, 130].

Li et al. bred Nod2–/– non-obese diabetic (NOD) mice with a different composition of gut microbiota compared to Nod2+/+NOD mice. The Nod2–/–NOD animal line appears to be more protected against diabetes and shows a significant decrease in pro-inflammatory cytokines coding immune cells and an increase in Tregs [137]. When mice of the Nod2–/–NOD line were co-housed with mice of the Nod2+/+NOD line, Nod2–/–NOD mice lost their protection against the development of type 1 diabetes. This suggests that the susceptibility of Nod2–/–NOD mice to type 1 DM depends on changes in the gut microbiota as it influences beta cells that produce immunoglobulin A (IgA), as well as the level of interleukin-10 (IL-10), which stimulates the activity of T-regulatory cells.

Several studies have investigated the role of adaptive immune cells in the pathogenesis of type 1 DM. There is evidence that beta cell damage occurs via $CD8^+$ cytotoxic T cells. Their abnormal activation is a consequence of molecular similarity and bacterial infections triggering the immune response. The possible role of TLRs is also discussed. pancreatic beta cells express TLR4, which make them sensitive to lipopolysaccharides (LPS), stimulating and activating the transcription of NF-κB-related pro-inflammatory genes that provoke an immune response against microbial invasion. Thus, the increased level of TLR4 is another mechanism for understanding the pathogenesis of type 1 DM [61].

MICROBIOTA CHANGES IN METABOLIC SYNDROME, TYPE 2 DIABETES MELLITUS

Metabolic syndrome is a symptom complex including visceral obesity, impaired glucose metabolism, dyslipidemia and arterial hypertension. Metabolic syndrome is associated with an increased risk of developing type 2 diabetes mellitus (type 2 DM) and cardiovascular pathology [49]. The disease is characterized by increased production of cytokines (mainly TNF-α and IL-1β) [118], and persistent inflammation [70].

The correlation between the gut microbiota, the pathogenesis of metabolic syndrome and type 2 DM was demonstrated by Guo et al. A line of obese mice demonstrated that diet can alter the gut microbial landscape as well as the production of antibacterial peptides associated with Paneth cells and even increase circulating pro-inflammatory cytokines such as TNF-alpha, IL-6 and IL-1beta [132]. Thus, it is diet-related gut dysbiosis, rather than adipose tissue itself, that plays a key role in the development of chronic intestinal inflammation [92].

Affecting energy production and storage, the gut microbiota can influence body weight and obesity, tissue pro-inflammatory activity, peripheral insulin resistance, pancreatic intestinal hormone production, and bile acid metabolism [63, 101]. Consequently, an increase in the Firmicutes/Bacteroidetes ratio corresponds to body weight and promotes hydrolysis of non-digestible polysaccharides in the intestine, which in turn contributes to an increase in calories extracted from food in metabolic syndrome [47, 88]. Several studies examining fecal samples from metabolic sydrome patients with type 2 DM have reported there is an increase in *Lactobacillales* with a decrease in *Roseburiaintestinalis*, *Faecalibacterium prausnitzii, Bacteroides*, *Prevotella genera*, *Bifidobacterium animalis* and *Methanobrevibacter smithii* compared to healthy subjects. Increased levels of Staphylococcus aureus, *Escherichia coli* and *Lactobacillus reuteri* may be associated with the development of obesity [84].

Tannerella spp. bacteria associated with oral infections and periodontal diseases provoke an increase in several pro-inflammatory cytokines

such as TNF-alpha, IL-1beta and IL-6 [116]. Lipopolysaccharide induced by Gram-negative bacteria is able to evoke an immune response through lipopolysaccharide-binding protein (LBP), which in turn binds the macrophage receptor CD14. The complex formed by lipopolysaccharide-lipoprotein-binding protein and CD14 can activate the pro-inflammatory genes NF-kB and AP-1 via TLR4 [74], and the absence of TLR4 protects against insulin resistance [114].

Gut dysbiosis can also mediate changes in the balance of Th17/Tregs cells. Thus, disruption of the physiologic balance between pro- and anti-inflammatory T cell subpopulations may be responsible for the development and progression of a number of inflammatory diseases, both gastrointestinal and systemic, including obesity-related metabolic syndrome and type 2 DM [70]. Thus, gut dysbiosis is closely associated with significant changes in the Th17/Tregs balance contributing to obesity, metabolic syndrome, and type 2 DM, allowing for new strategies for the treatment of the aforementioned diseases.

CHANGES IN THE MICROBIOTA IN PANCREATIC TUMORS

Pancreatic cancer is an aggressive disease with an uncertain prognosis. By the time of the diagnosis, only 25% of pancreatic cancer cases are amenable to radical surgical treatment. About 95% of cases are adenocarcinomas derived from glandular, ductal or acinar cells of the exocrine pancreas [6].

An association between dysbacteriosis, chronic inflammation and pancreatic cancer has been established [17–24], but dysbacteriosis does not have direct effects that disrupt cell cycle control, activate oncogenic signaling pathways and produce tumor metabolites [41–85]. However, gut dysbiosis can activate the immune system through several pathways that include tumor-infiltrating lymphocytes (TILs) and their associated cytokines, innate immune cells, TLRs, and others. Thus, TILs produce pro-inflammatory mediators that induce STAT3 and NF-κB pathways, which act as oncogenic factors by enhancing cell proliferation and inhibiting apoptosis [15–98].

Several microbe-free mouse lines have made it possible to understand the significant role of the gut microbiome which influence carcinogenesis. The probability of cancer development is significantly reduced, possibly due to the absence of gut dysbiosis and associated chronic inflammation [135]. A similar effect was found in mice after antibiotic treatment, which may indicate a reduced influence of pathogens in the intestinal mucosa [24]. Other experimental evidence suggests a close association between diet, xenobiotics, gut microbiota and cancer [20]. One study found an increased risk of tumor development in mice that were genetically predisposed to colorectal cancer and had a certain composition of gut microflora. This tumor predisposing phenotype could be transferred to healthy mice after microbiota transplantation using fecal samples. Interestingly, antibiotics were able to limit tumor development, likely by blocking the intestinal gut microbiota in the mice. Boursi et al. performed a large population-based study showing that repeated exposure to antibiotics, particularly penicillin, may contribute to the development of esophageal, gastric, pancreatic, and rectal cancers, probably due to changes in the microbiota [4].

In chronic pancreatitis, people with KRAS mutation have an increased risk of pancreatic cancer [9, 95, 131, 132], and gut dysbiosis can accelerate pancreatic carcinogenesis through mutated KRAS hyperstimulation [40, 43]. Gram-negative LPS-TLR4 was linked in inducing chronic inflammation and cancer as well [56]. Ochi et al. experimentally discovered the influence of lipopolysaccharides in the pathogenesis of pancreatic cancer [56]. LPS administration in mice was able to significantly accelerate carcinogenesis, while TLR4 inhibition limited cancer progression.

Bacterial pathogens are capable of acting as carcinogenic factors. Among them, *Helicobacter pylori* plays a special role [79], which can promote gastric, liver and pancreatic cancer by inducing activation of nuclear factor NF-κB and its pro-inflammatory cytokines such as IL-1β [53]. Some Fusobacterium species have also been associated with the development of pancreatic cancer, and they are associated with worse prognosis [138].

Ren et al. found decreased microbiota diversity in 85 pancreatic cancer patients compared to 57 healthy individuals [22]. Patients with pancreatic tumor have a specific microbial profile characterized by an increased presence of some pathogens such as *Veillonella*, *Klebsiella* and *Selenomonas*, as well as bacteria capable of producing lipopolysaccharides (LPS) including *Prevotella, Hallella* and *Enterobacter*. Related to this, there was a decrease in some commensal microorganisms, such as *Bifidobacterium*, and a decrease in bacteria that produce butyrate, such as *Coprococcus, Clostridium IV, Blautia, Flavonifractor* and *Anaerostipes*. Evidence of an increase in LPS-producing bacteria supports the role of dysbiosis in mediating chronic inflammation and oxidative

damage, activating the NF-κB pathway and associated production of pro-inflammatory cytokines. Thus, prolonged chronic inflammation and oxidative damage provoke carcinogenesis.

In addition, pancreatic cancer correlated with a change in the physiological composition of the oral microbiota towards predominance of microbial associations associated with periodontal diseases [45]. Farrell et al. performed a study analyzing the salivary microbiota of several patients with pancreatic cancer and chronic pancreatitis compared to healthy controls. The researchers found specific changes in the composition of the salivary microbiota (decrease in *Neisseria elongata, Corynebacterium* spp. and *Streptococcus mitis* and increase in *Granulicatella adiacens* and *Porphyromonas gingivalis*) [45, 46]. Torres et al. conducted a cross-sectional study showing an increase in *Leptotrichia* spp. and a decrease in *Porphyromonas* spp. in the saliva of a pancreatic cancer patient; thus, a higher *Leptotrichia / Porphyromonas (L/P)* ratio may be an important biomarker for the diagnosis of pancreatic cancer [19]. Michaud et al. found that the highest concentration of serum antibodies to *Porphyromonas gingivalis* bacteria (associated with periodontal disease) was associated with a twofold increased risk of pancreatic cancer [35], which can be used as a tool to detect early pancreatic cancer using blood, saliva and fecal samples. However, further studies on the relationship of gut microbial changes in the mechanism of pancreatic cancer are required.

In conclusion, pancreatic cancer is considered an insidious and aggressive disease characterized by late diagnosis and lack of effective screening methods. The use of gut microbiome modulation for therapeutic purposes is unlikely in general clinical practice; however, the determination of the gut microbiocenosis pattern may become a diagnostic tool in predicting the development of pancreatic cancer, thereby improving survival rates.

CONCLUSIONS

The gut microbiota plays a central role in the development and modulation of gut homeostasis and mucosal immune system integrity. It plays an important role in protection against pathogenic microbes by maintaining gut integrity and regulating the permeability of the intestinal barrier.

The pancreas does not possess its own microflora, and evidence suggests that alteration of the gut microbiota, which determines dysbiosis and bacterial translocation, correlates with the duration and prognosis of several pancreatic diseases, including pancreatitis, diabetes, and cancer. However, it remains unclear whether gut dysbiosis is a cause or a consequence of such pathologic conditions.

ADDITIONAL INFORMATION

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PROMISING AREAS OF SCIENTIFIC RESEARCH ON THE PROBLEMS OF INTESTINAL INFECTIONS

© Natalya V. Gonchar[1, 2], Nataliya V. Skripchenko[2, 3]

[1] North-Western State Medical University named after I.I. Mechnikov. Kirochnaya str., 41, Saint Petersburg, Russian Federation, 191015
[2] Children's Research and Clinical Center for Infectious Diseases of the FMBA of Russia. Professor Popov str., 9, Saint Petersburg, Russian Federation, 197022
[3] Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Natalya V. Gonchar — MD, PhD, Doctor of Medical Sciences, Professor, Department of Pediatrics and Neonatology; Leading Researcher. E-mail: nvgonchar@yandex.ru ORCID: 0000-0002-5938-2934

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Abstract. The solution of modern problems of diagnosis and treatment of intestinal infections in children is determined by the most important areas of scientific research, among which are the molecular genetics and clinical features of viral diarrhea pathogens, improvement of therapy methods for acute gastroenteritis of viral etiology, molecular diagnostics of toxin-producing bacterial intestinal pathogens, biological safety and intestinal infections, prediction of antibiotic-associated diarrhea and treatment approaches, clinical significance of diarrhea of conditionally pathogenic bacterial etiology in children, antibiotic resistance of *Enterobacteriaceae* and the effectiveness of phage therapy, personalized symbiont therapy of convalescents of intestinal infections.

***Key words*:** *intestinal infections; children; etiology; diagnosis; treatment*

ПЕРСПЕКТИВНЫЕ НАПРАВЛЕНИЯ НАУЧНЫХ ИССЛЕДОВАНИЙ ПО ПРОБЛЕМАМ КИШЕЧНЫХ ИНФЕКЦИЙ

© Наталья Васильевна Гончар[1, 2], Наталия Викторовна Скрипченко[2, 3]

[1] Северо-Западный государственный медицинский университет им. И.И. Мечникова. 191015, г. Санкт-Петербург, ул. Кирочная, 41
[2] Детский научно-клинический центр инфекционных болезней ФМБА России. 197022, г. Санкт-Петербург, ул. Профессора Попова, 9
[3] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Наталья Васильевна Гончар — д.м.н., профессор кафедры педиатрии и неонатологии; ведущий научный сотрудник.
E-mail: nvgonchar@yandex.ru ORCID: 0000-0002-5938-2934

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Резюме. Решение современных проблем диагностики и лечения кишечных инфекций у детей определяет важнейшие направления научных исследований, в ряду которых стоят молекулярно-генетические и клинические особенности возбудителей вирусных диарей, совершенствование методов терапии острых гастроэнтеритов вирусной этиологии, молекулярная диагностика токсинпродуцирующих бактериальных кишечных патогенов, биологическая безопасность и кишечные инфекции, прогнозирование антибиотик-ассоциированной диареи и подходы к лечению, клиническое значение диареи условно-патогенной бактериальной этиологии у детей, антибиотикорезистентность энтеробактерий и эффективность фаготерапии, персонифицированная симбионтная терапия реконвалесцентов кишечных инфекций.

Ключевые слова: *кишечные инфекции; дети; этиология; диагностика; лечение*

RELEVANCE OF RESEARCH ON THE PROBLEMS OF ACUTE INTESTINAL INFECTIONS

The years 2022–2031 have been declared the Decade of Science and Technology in Russia (Decree of the President No. 231, April 25, 2022). The aim of the Decade is to strengthen the role of science and technology in solving the most important problems of the development of society and country.

The relevance of scientific research on the problems of acute intestinal infections (AII) in the world is confirmed by statistical data on scientific publications in PubMed for the last 10 years, indicating an increase in the number of annual publications devoted to acute gastroenteritis. Also there was no decrease in number of publications devoted to rotavirus and norovirus gastroenteritis, as well as salmonellosis (Fig. 1).

The topics of publications and thesises allow us to identify the following priority areas of scientific research on the problems of AII in children in the domestic and foreign literature: Molecular genetic characteristics and clinical picture of intestinal infections of viral etiology [1–4]; intestinal infections of bacterial etiology (typhoid fever, shigellosis, salmonellosis) [5–10]; intestinal infections caused by opportunistic Enterobacteriaceae [11, 12]; healthcare-associated viral intestinal infections [13, 14]; immunopathogenesis, gut microbiota and optimization of therapy for intestinal infections [15–17].

Acute gastroenteritis. Norovirus gastroenteritis in children. Rotavirus gastroenteritis in children. Salmonellosis in children.

MOLECULAR GENETIC FEATURES OF VIRAL PATHOGENS CAUSED DIARRHEA

The relationship between molecular genetic features of viral pathogens caused diarrhea and severity of clinical manifestations of the disease is being actively studied. Thus, comparison of the genetic structure of circulating rotavirus strains in Qatar [18] and Indonesia [19] in 2015–2019 years revealed the similarity of dominant genotypes — G3P [8]. According to the Vesikari scale for severity of AII, severe forms of rotavirus infection in Qatar, including diarrhea and vomiting, were most frequently caused by G3P [8], and less frequently caused by other genotypes.

The study of molecular epidemiology of rotavirus infection have practical implications: in the East Java region (Indonesia), in September 2015 — March 2018 [19], a shift from group A rotavirus equine-like strains (G3) to human strains (G1/G3) was observed amid a sharp drop in rainfall intensity (Figure 2). Comparison of the population of group A rotavirus (RVA) genotypes by whole genome sequences in different periods of the study shows differences in the set of genome segments during the change of genotypes (Fig. 3).

According to the results of observations of the Reference Center for Monitoring of Acute Intestinal Infections, in the Russian Federation in 2021 [20]

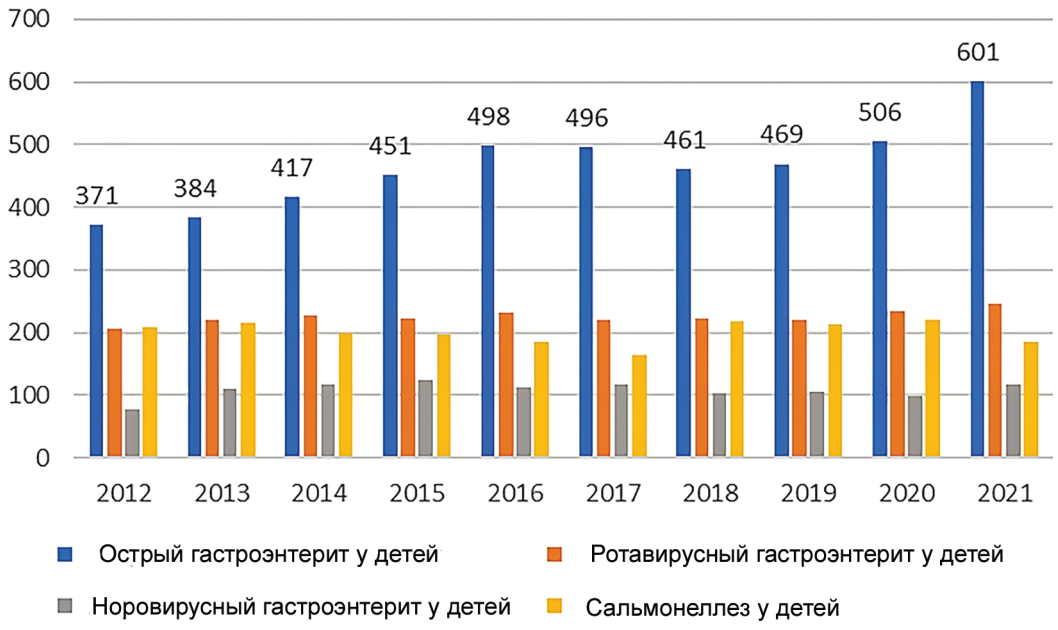

Fig. 1. Number of annual publications on "Acute intestinal infections in children" in PubMed (2012–2021)
Рис. 1. Число ежегодных публикаций по теме «Острые кишечные инфекции у детей» в PubMed (2012–2021)

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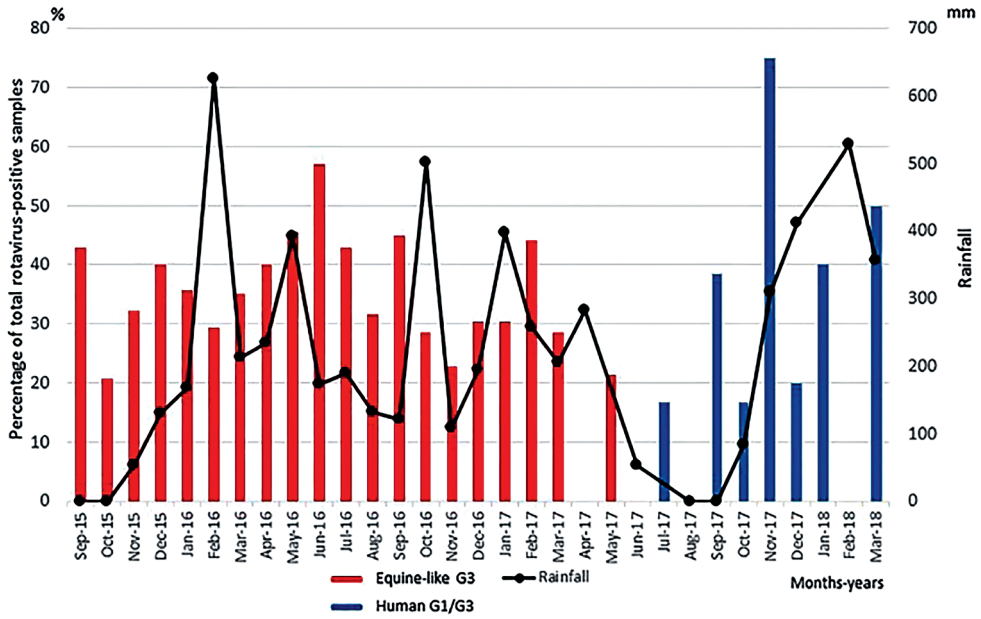

Fig. 2. Frequency of isolation of group A rotavirus equine-like strains (G3) and human strains (G1/G3) in East Java region from September 2015 to March 2018 [19]

Рис. 2. Частота выделения лошадиноподобных штаммов ротавируса группы А (G3) и человеческих штаммов (G1/G3) в регионе Восточной Явы в период с сентября 2015 г. по март 2018 г. [19]

Name of strain	Genotypes										
	VP 7	VP4	VP6	VP1	VP2	VP3	NSP1	NSP2	NSP3	NSP4	NSP5
RVA/Hu-tc/USA/Wa/1974/G1P1A[8]	G1	P[8]	I1	R1	C1	M1	A1	N1	T1	E1	H1
RVA/Hu-tc/USA-DS-1/1976/G2P[4]	G2	P[4]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/D05/2013/G1P[8]	G1	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/D13/2013/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/D37/2013/G1P[8]	G1	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/D63/2013/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/GRV60/2014/G1P[8]	G1	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/GRV67/2014/G1P[8]	G1	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/GRV68/2014/G1P[8]	G1	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM004/2015/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM008/2015/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM009/2015/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM044/2015/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM050/2015/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM102/2016/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM147/2016/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM169/2016/G3P[6]	G3	P[6]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM182/2016/G3P[6]	G3	P[6]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM197/2016/G3P[6]	G3	P[6]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM230/2016/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM369/May2017/G3P[8]	G3	P[8]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM387/July2017/G1P[8]	G1	P[8]	I1	R1	C1	M1	A1	N1	T1	-	H1
RVA/Human/IDN/STM415/2017/G3P[6]	G3	P[6]	I2	R2	C2	M2	A2	N2	T2	E2	H2
RVA/Human/IDN/STM453/2018/G1P[8]	G1	P[8]	I1	R1	C1	M1	A1	N1	T1	E1	H1
RVA/Human/IDN/STM457/2018/G1P[8]	G1	P[8]	I1	R1	C1	M1	A1	N1	T1	E1	H1

Fig. 3. Comparison of the population of RVA genotypes by whole genome sequences in different periods of the study (23 Indonesian strains) [19]

Рис. 3. Сравнение совокупности генотипов RVA по последовательностям всего генома в разные периоды исследования (23 индонезийских штамма) [19]

the prevalence of the G9P [8] genotype was maintained and proportion of the G3P [8] genotype of rotaviruses increased. Among the genotypes that do not have a global distribution, circulation of the G8P [8] genotype has been established.

Against the background of an introduction of routine rotavirus vaccination, the study of genotypic and clinical features of norovirus infection (NVI) is important. The structure of circulating norovirus strains in many countries is dominated

by the GII strain, but data on the clinical features of NVI caused by the same strains of the pathogen vary from country to country. For example, in Ghana, the clinical picture of NVI in children infected with GII.4 and non-GII.4 strains did not differ [21], and in children in Canada, the clinical picture of NVI caused by GII.4 strain was characterized by higher scores on Vesikari scale and longer duration of diarrhea and vomiting compared with the clinical picture of NVI caused by non-GII.4 strains [22].

The genomic organization of the genus *Norovirus* is being studied. Norovirus RNA contains three open reading frames that encode eight viral proteins (https://viralzone.expasy.org/194). The first classification of the genus Norovirus is based on the assessment of nucleotide sequence diversity obtained by sequencing the ORF 1 or ORF 2 regions. In 2013, a universal standardized system of norovirus nomenclature and typing was proposed, according to which, in 2019, 10 genogroups (GI-GX) and 48 genotypes were distinguished, and changes were made to the designation of norovirus strains because frequent recombination events in the norovirus genome cause data on the number of genotypes quickly become outdated. The diversity of circulating norovirus genotypes, rapid variability of the genome, and Its ability to cause outbreak morbidity indicate the need for continuous monitoring of NVIs [23].

According to the observations of the Reference Center for Monitoring of Intestinal Infections, in the Russian Federation in 2021 [20], genotypes / genogroups of noroviruses in foci of group and sporadic morbidity differ. The results of genotyping of isolates in outbreak and sporadic morbidity indicate the diversity of norovirus genotypes / genogroups.

INTESTINAL INFECTIONS CAUSED BY UNIDENTIFIED PATHOGENS

Intestinal infections caused by unidentified pathogens are characterized by significant medical, social and economic importance, and Its morbidity rates have remained high for many years [20]. It accounts for more than 30% in the etiologic structure of AII according to data of Children's research and clinical center for infectious diseases of the FMBA of the Russian Federation. Reducing the proportion of infectious diarrheas of unidentified etiology can be achieved by expanding the range of diagnosable pathogens.

In recent years, the number of studies demonstrating the association of acute gastroenteritis (AGE) with "non-intestinal" adenoviruses have increased worldwide. The etiologic role of adenovirus genotype B3 has been proven in infants and children with diarrhea; genotypes C1, C2, and C5 are also frequently identified in patients with AGE. In addition, genotypes A12, A18, A31 and G52 are capable of causing symptoms of AGE [24]. In Italy, the incidence of adenoviral gastroenteritis in hospitalized children is 7.1%, which is consistent with the results of studies in Thailand, Japan, China and India. A predominance of adenovirus genotypes C (91.2%) and B (8.8%) was detected by molecular typing. However, F40 and F41 genotypes, which are most common in patients with AGE, were not identified in this study [25]. Since most commercial systems detect only the "intestinal" strains F40 and F41, new rapid and reliable detection methods should be developed for all known adenovirus genotypes at present.

Human parechoviruses (HPeV), which, like enteroviruses (EV), are members of the family *Picornaviridae*, should also be considered in the verification of viral diarrhea. The genus *Parechovirus* is divided into 2 species: *Parechoviruses* A and B. *Parechovirus* A species consists of 16 types [26].

The incidence of parechovirus infection is not precisely known because it is not reportable, but is assumed to correspond to the incidence of enterovirus infection [26]. Unlike EV infection, HPeV infection is rare in older children and adults. Serologic data show that more than 90% of children under 2 years of age are infected with at least one type of HPeV. The primary sites of EV and HPeV replication are epithelial cells of the oropharynx and intestinal mucus membrane, followed by viremia and secondary infection of various organs and tissues. Most studies have focused on the pathogenicity of HPeV genotypes 1 and 3. The clinical manifestations due to different HPeV genotypes are thought to be due to differences in their biological properties. Most commonly, circulating HPeV genotype 1 causes mild gastrointestinal and respiratory complaints, although more severe disease may be detected in young children. HPeV genotype 3 is a more pathogenic type associated with paralysis, neonatal sepsis and sudden death in infants [27]. The PCR-RT method is recognized as the "gold standard" for the diagnosis of HPeV infection [26].

PROBLEMS OF TREATMENT FOR ACUTE GASTROENTERITIS AND ROTAVIRUS VACCINATION

Probiotics are used as medicines that can accelerate the symptomatic relief of acute gastroenteritis. However, recent clinical studies have questioned their efficacy [28]. It was shown that there were no differences in the efficacy of treatment for AII of viral, bacterial, and combined viral-bacterial

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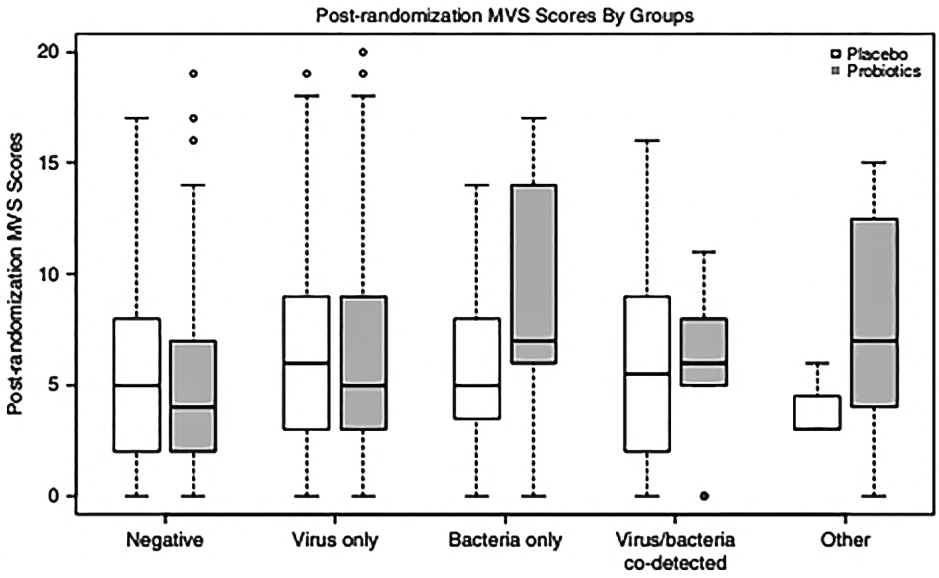

Fig 4. Comparison of severity of acute gastroenteritis according to the Vesikari scale in children (n=816) in groups with different treatment (5-day use of probiotics *L. rhamnosus+L. helveticus* or placebo) and groups with diseases of different etiology [28]

Рис. 4. Сравнение тяжести острых гастроэнтеритов по шкале Везикари у детей (n=816) по группам лечения (5-дневный прием пробиотиков *L. rhamnosus+L. helveticus* или плацебо) и группам этиологии заболевания [28]

etiologies, previously vaccinated against rotavirus infection, according to the criteria for assessing a severity of the disease (Vesikari scale). It was shown in group of children who were treated with a 5-day course of probiotics (*L. rhamnosus+L. helveticus*) and in group of children treated with platinum-based probiotics (*L. rhamnosus+L. helveticus. Helveticus*) and in the placebo group (Fig. 4). Also, the absence of differences in the terms of norovirus elimination was established, when assessment of dynamics and count of norovirus in faces in three described groups was done.

The explanation for these facts may be the change of leading pathogens after routine use of rotavirus vaccine and insufficient study of the therapeutic effects of probiotics in AGE of non-rotavirus etiology.

The analysis of changes in fecal viral load in patients with AGE represents a new unique approach to diagnosis and assessment of therapy efficacy. A higher viral load reflects a greater degree of intestinal epithelial damage and contributes to the development of a more severe disease [29]. A high viral load in feces of patients does not exclude the possibility of intestinal viruses spreading outside the intestine into the bloodstream (viral antigenaemia) and manifestation of extraintestinal signs of AGE [30].

New strategies for the prevention and treatment of viral diarrhea are being developed. It has been established that certain representatives of the gut microbiota are capable of exerting an inhibitory or stimulatory effect on the infectivity of intestinal viruses *in vitro*. In particular, it has been shown that the bacterial taxa *Ruminococcus* and *Oxalobacter* can inhibit rotavirus infection [31].

ISSUES OF ETIOLOGY OF FOODBORNE INTOXICATION

As it was noted in the State Report of Russian Agency for Health and Consumer Rights, the incidence of foodborne intoxication of unspecified etiology in the Russian Federation, in 2021–2020, increased by 17.5%, not exceeding the average annual level (336.11) [20]. Also, in 2020, botulism affected 112 people, 7 of them had a fatal outcome. In the first 9 months of 2021, botulism affected 92 people, in whom 15 cases were fatal. Botulism develops by eating products containing toxin produced by vegetative forms of *Clostridium botulinum*, characterized by paresis and paralysis of striated and smooth muscles, which in the initial period of the disease is sometimes accompanied by gastroenteritis. The infectious nature of the disease is clearly manifested in cases of botulism in children of the first year of life and in extremely rare cases of botulism in adults, when the incubation period exceeds 4–5 days [32].

The control of foodborne intoxication is accompanied by measures on hygiene of children's food, implemented through the system of dissemination of medical knowledge. Molecular diagnostics of toxin-producing intestinal pathogens in contaminated food for children's feeding play an important role and make it possible

to significantly increase the etiologic interpretation of infections caused by toxin-producing bacteria [3].

BIOSECURITY AND INTESTINAL INFECTIONS

The VII (current) cholera pandemic began in 1961 in South Asia, spread to Africa in 1971, and to America in 1991. Currently, cholera is an endemic disease (in 2020, 323,369 cases were registered in 24 countries). In Mariupol, the first 3 cases of cholera were reported on May 29, 2011, and the outbreak ended on August 19. Laboratory tests confirmed 54 cases, including 22 cases of carriage. A toxigenic strain of *V. cholera eltor* of Ogawa serovar, resistant to tetracycline and levomycetin, was isolated in all infected persons. The most important factors of cholera transmission were fish cutting and eating (48.1% cases in total) [33]. The annual isolation of non-toxigenic *V. cholera* indicates the need to determine the potential and real risks of contamination of water with V. cholera of O1/O139 serogroups and elimination of pathogens [34].

PREDICTION PROBLEMS, ETIOLOGY AND TREATMENT APPROACHES FOR ANTIBIOTIC-ASSOCIATED DIARRHEA

The study of a heterogeneity of diarrhea in 981 patients with COVID-19 allowed us to distinguish early antibiotic-associated diarrhea (AAD) — viral etiology (9.3% of patients) and late AAD — bacterial etiology (16.7% of patients). This fact suggests the use of different methods of treatment [35]. Toxin-producing *C. difficile* strains were detected in 70.5% of adult patients with COVID-19 and late diarrhea, but it was not found in patients with early diarrhea. Risk factors for the development of late AAD were identified: use of oral amoxiclav (OR=2.2) or clarithromycin (OR=3.8), and glucocorticoids (OR=4.4). Late AAD was associated with an increased risk of death after 20 days of illness (OR=4.7). Before the development of late AAD, the decrease in C-reactive protein level and increase in the number of lymphocytes stopped, but the number of leukocytes and neutrophils in the blood increased (sensitivity 82.0%, specificity 70.8%).

According to modern studies, the frequency of detection of toxin-producing *C. difficile, C. perfringens, K. oxytoca*, and *S. aureus* during AAD in hospitalized adult patients is 19.6, 14.9, 27, and 5.2%, respectively. At the same time, high resistance of *C. difficile* was found to ciprofloxacin, and low resistance to chloramphenicol, vancomycin, and metronidazole [36].

Nowadays, new methods of treatment for antibiotic-associated colitis associated with *C. difficile* are being developed and implemented — transplantation of intestinal microbiota of healthy donors [37].

DIARRHEA OF OPPORTUNISTIC ETIOLOGY IN CHILDREN

AII caused by opportunistic Enterobacteriaceae (OE) in children under 1 year of age account for 60% of the total number of AIIs of specified bacterial etiology [38], where *Klebsiella pneumoniae* plays a leading role among the causative agents [39]. OE diarrhea more often proceeds as a mild monoinfection [38].

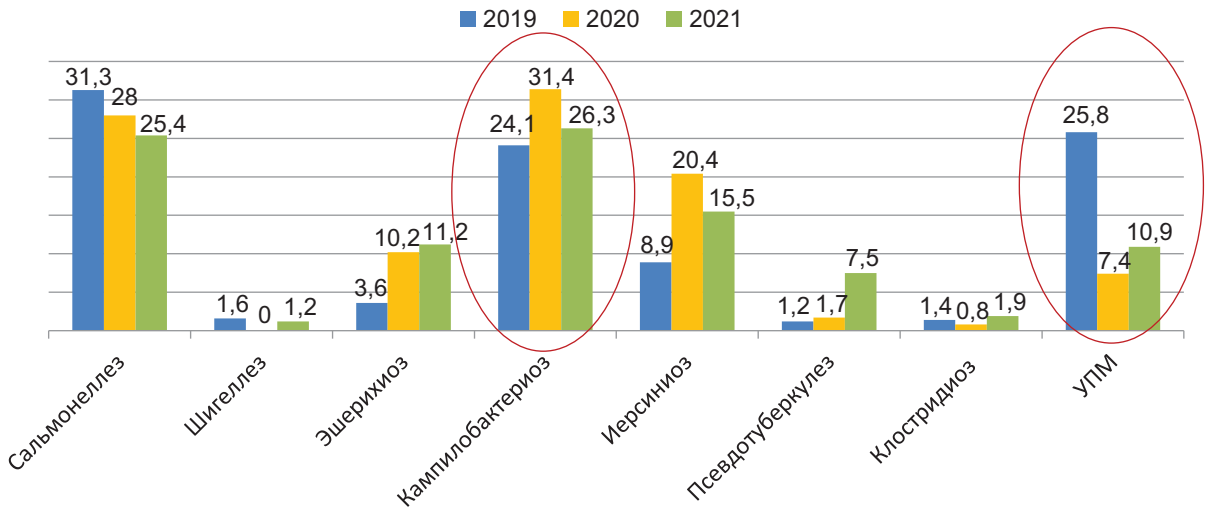

Fig. 5. Dynamics of frequency of diagnostics of bacterial AII of different etiology in children in Children's Research and Clinical Center for Infectious Diseases of the FMBA of the Russian Federation in 2019–2021. OM — opportunistic microbes

Рис. 5. Динамика частоты диагностики бактериальных ОКИ различной этиологии у детей в ДНКЦИБ ФМБА России в 2019–2021 гг. УПМ — условно-патогенные микробы

Klebsiellosis is more common in young children with an unfavorable premorbid background: protein-energy malnutrition, rickets, deficiency anemia. Patients under 1 year of age are characterized by water loss dehydration [40].

Analysis of the dynamics of the frequency of diagnosis of bacterial AII of various etiologies in children in the Children's research and clinical center for infectious diseases of FMBA of the Russian Federation in 2019-2021 shows that AII caused by opportunistic pathogenic microbes (APM) is detected almost as often as campylobacteriosis (Fig. 5).

ANTIBIOTIC RESISTANCE OF ENTEROBACTERIACEAE AND PHAGE THERAPY

Antibiotic-resistant Enterobacteriaceae (ESCAPE pathogens: *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. Aeruginosa, Enterobacter*) became a global problem of the Health care. Antibiotic susceptibility testing of 646 Enterobacteriaceae isolates revealed multidrug resistance in 87.3% of cases. β-lactamase genes were detected in 73.2% of isolates [41].

Phages and phage-encoded enzymes are used as etiological therapy for antibiotic-resistant pathogens, which is based on the principles of interaction between phages, pathogenic bacteria, and immune cells (Fig. 6) [42].

TRENDS IN GROWTH OF PHAGORESISTANCE OF OPPORTUNISTIC ENTEROBACTERIACEAE

In children with impaired gut microbiota, there is a significant frequency of detection of phage-resistant strains of OP. That is why a regular monitoring of sensitivity of these strains to bacteriophages is necessary to improve the effectiveness of phagotherapy prescribed to infants and young children. Data on the sensitivity of OPs to bacteriophages are not stable and may vary depending on the frequency of antimicrobial use in the region. Studies indicate a rather large proportion of OPs (43.5%) resistant to bacteriophages [43].

New therapeutic approaches to overcome phage resistance in OPs are being developed. There is evidence that the use of a combination of an antibacterial drug or antibiotic with bacteriophages increases the effectiveness of treatment for staphylococcal enterocolitis in infants [38].

IMPROVEMENT OF PATHOGENETIC AND ETIOTROPIC THERAPY FOR ACUTE INTESTINAL INFECTIONS IN CHILDREN

The prospect of new nutritious low-osmolar rehydration mixtures and new enterosorbents-cytomucoprotectors in treatment of children with viral diarrhea has been demonstrated. The use of nutritious low-osmolar rehydration mixtures and cytomucoprotector in children with AII has a rapid detoxification and antidiarrheal effect [44].

Studies aimed at research of nutritional status in children with infectious diarrhea as a criterion of premorbid background, the dynamics of course of the disease and as a basis for optimizing therapeutic nutrition are relevant. The correlation between severity of infectious colitis and nutritional disorders in children of different age groups was shown [45].

The issues of etiological therapy of campylobacteriosis and its influence on clinical manifestations and gut microbiota in children are studied. It was shown in studies, that in the treatment for severe and moderate-to-severe forms of campylobacteriosis in children, antibacterial drugs of the macrolide group were more effective. The use of

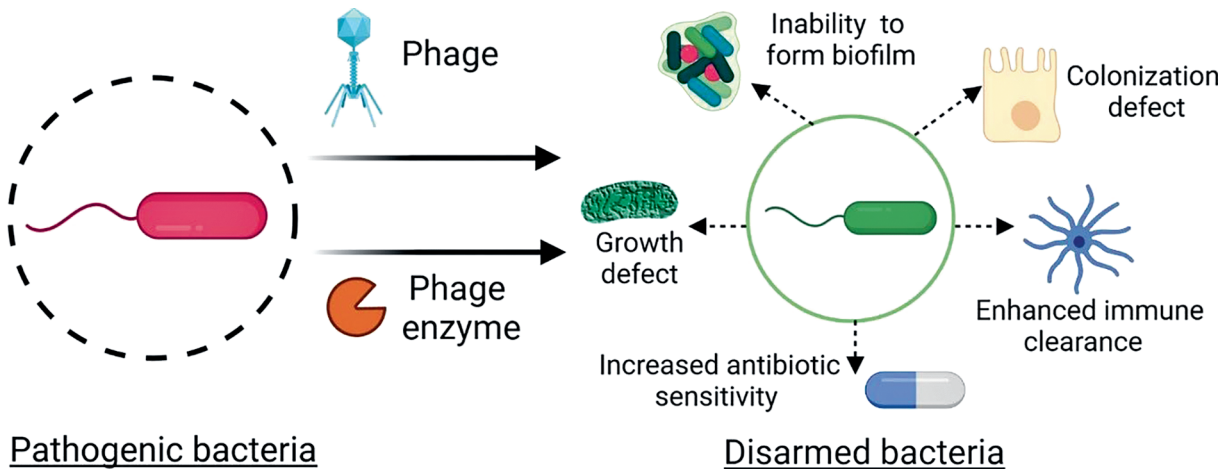

Fig. 6. Scheme of interaction between phages, pathogenic bacteria and immune cells [42]

Рис. 6. Схема взаимодействия между фагами, патогенными бактериями и иммунными клетками [42]

cephalosporins leads to delayed recovery due to significant damage of a gut microbiota [46].

The personalized symbiont therapy of children who had had an AII based on the use of autoprobiotics for the prevention of postinfection gastroenterological pathology is being developed. The introduction of targeted probiotics (autoprobiotics) for the correction of disorders of gut microbiota in children with prolonged course of intestinal infections is a promising way to improve the effectiveness of treatment and prevention of postinfection functional gastroenterological pathology [47].

CONCLUSION

The relevance of scientific studies on the problems of acute intestinal infections in children is beyond doubt. Promising areas of research today are molecular and genetic features of pathogens, which causes a viral diarrhea, improvement of therapy methods for acute gastroenteritis of viral etiology, molecular diagnostics of toxin-producing bacterial pathogens, biosafety and intestinal infections, prediction of antibiotic-associated diarrhea and approaches to treatment, clinical significance of diarrhea of opportunistic etiology in young children, antibiotic resistance of Enterobacteriaceae and the effectiveness of antibiotic therapy. The introduction of scientific and technical progress in medicine contributes to the improvement of diagnosis, treatment and prevention of infectious diseases.

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.

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

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DATA OF DISPENSARY EXAMINATION OF TEENAGERS IN THE SHALINSKY DISTRICT OF THE REPUBLIC OF CHECHNYA

© Dmitry O. Ivanov, Vera L. Gritsinskaya, Liliya V. Ditkovskaya, Anna V. Mironova, Yulia L. Skorodok, Elena V. Kurchina, Leonid A. Kornievsky, Andrey Yu. Baranov, Ivan G. Vodyanikov

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Vera L. Gritsinskaya — Doctor of Medical Sciences, Leading researcher of the laboratory of medical and social problems in Pediatrics of scientifical researching center. E-mail: tryfive@mail.ru ORCID: 0000-0002-8290-8674 SPIN 7966-9470

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Abstract. *Introduction.* Detection of early deviations in health is possible during preventive medical examinations. *Purposes and tasks:* assessment of the health status of schoolchildren in the Republic of Chechnya. *Material and methods.* Within the framework of the clinical examination, 327 secondary school students of the Shali region (138 girls and 189 boys) aged from 14 to 17 were examined. Completed: somatometry; examination by a pediatrician, pediatric endocrinologist, obstetrician-gynecologist, otorhinolaryngologist, pediatric dentist, ophthalmologist, pediatric surgeon, pediatric urologist-andrologist and orthopedic traumatologist. The assessment of physical development is given according to the standards "WHO Growth Reference 2007". *Results.* Average physical development was in 78.3±2.3% of schoolchildren; harmonious — in 60.4±2.7% of students. Disharmonious variants of physical development caused by a deficit in body weight were observed more often (21.7±2.3%) than those caused by excess nutrition (17.9±2.4%). A high prevalence of endemic goiter was revealed (28.3±2.4%); dental caries (65.1±2.6%); posture disorders (32.1±2.5%); chronic tonsillitis (36.8±2.7%); decrease in visual acuity (33.1±2.6%); various options for menstrual irregularities (in 54.3±4.2% of girls). According to the dispensary examination, the II health group was identified in 66.6±3.4% of boys and 65.2±4.1% of girls; Group III in 33.4±3.4% and 34.8±4.1%, respectively. *Conclusion*. Analysis of the data obtained allows planning measures for further examination, treatment, rehabilitation and dispensary observation of students in the Shali district of Chechnya.

Key words*: children; schoolchildren; medical examination; Chechnya*

ДАННЫЕ ДИСПАНСЕРНОГО ОСМОТРА ПОДРОСТКОВ В ШАЛИНСКОМ РАЙОНЕ РЕСПУБЛИКИ ЧЕЧНЯ

© Дмитрий Олегович Иванов, Вера Людвиговна Грицинская, Лилия Викторовна Дитковская, Анна Валерьевна Миронова, Юлия Леонидовна Скородок, Елена Валерьевна Курчина, Леонид Александрович Корниевский, Андрей Юрьевич Баранов, Иван Геннадьевич Водяников

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Вера Людвиговна Грицинская — д.м.н., ведущий научный сотрудник лаборатории медико-социальных проблем в педиатрии научно-исследовательского центра. E-mail: tryfive@mail.ru ORCID: 0000-0002-8290-8674 SPIN 7966-9470

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Резюме. *Введение.* Выявление ранних отклонений в состоянии здоровья возможно при проведении профилактических медицинских осмотров. *Цель исследования*: оценка состояния здоровья школьников в Республике Чечня. *Материал и методы*. В рамках диспансеризации было осмотрено 327 учащихся средних школ Шалинского района (138 девочек и 189 мальчиков) в возрасте от 14 до 17 лет. Проведено: соматометрия; осмотр педиатра, детского эндокринолога, акушера-гинеколога, оториноларинголога, детского стоматолога, офтальмолога, детского хирурга, детского уролога-андролога и травматолога-ортопеда. Оценка физического развития дана по нормативам WHO Growth Reference 2007. *Результаты.* Среднее физическое развитие было у 78,3±2,3% школьников; гармоничное — у 60,4±2,7% учащихся. Дисгармоничные варианты физического развития, обусловленные дефицитом массы тела, отмечались чаще (21,7±2,3%), чем обусловленные избыточным питанием (17,9±2,4%). Выявлена высокая распространенность эндемичного зоба (28,3±2,4%), кариеса зубов (65,1±2,6%), нарушения осанки (32,1±2,5%), хронического тонзиллита (36,8±2,7%), снижения остроты зрения (33,1±2,6%), различных вариантов нарушения менструального цикла (у 54,3±4,2% девочек). По данным диспансерного осмотра определена II группа здоровья — у 66,6±3,4% мальчиков и 65,2±4,1% девочек; III группа — у 33,4±3,4% и 34,8±4,1% соответственно. *Заключение.* Анализ полученных данных позволяет спланировать мероприятия по дальнейшему обследованию, лечению, реабилитации и диспансерному наблюдению учащихся Шалинского района Чечни.

Ключевые слова*: дети; школьники; диспансеризация; Чечня*

Preserving the health in children is possible with use of active detection of the initial stages of diseases, timely prescription of optimal treatment and preventive measures. The influence of numerous environmental factors may have a significant impact on growth, development and morbidity in children and adolescents [1–4]. The priority direction of medical care for the children of the country is mass preventive examinations [5, 6]. Preventive measures in children and adolescents in the Russian Federation are currently regulated by the order of the Ministry of Health care of the Russian Federation, 10.09.2017 № 514n "On the order of preventive medical examinations of minors", approved by the Ministry of Justice of the Russian Federation, which came into force on January 1, 2018. Preventive measures involve examination by doctors of different specialties, laboratory and instrumental methods [7, 8]. Effective medical examination is most relevant in the regions densely populated by indigenous peoples of the country [9, 10].

The Republic of Chechnya is located in the south of the European part of the Russian Federation in the eastern part of the North Caucasus. The Shalinskij District is located in the central part of the republic, in the foothill zone. The climate in the district is temperate continental. According to the State Report "On the State of Sanitary and Epidemiological Well-Being of the Population in the Russian Federation in 2012", the Shalinskij District, like the rest of the country, has a moderate continental climate. Shalinskij district, as well as the entire territory of the republic, was classified as a region with a naturally occurring iodine deficiency.

In order to assess the state of health of the population, employees of the St. Petersburg State Pediatric Medical University visited the Republic of Chechnya to conduct preventive examinations of children together with the republic's physicians.

We examined 327 secondary school students of Shalinskij district (138 girls and 189 boys) aged from 14 to 17 years as part of the medical examination. After signing the informed consent, we analyzed medical records (form 026y) and conducted a clinical examination of adolescents. Doctors of different specialties took part in the medical examination: pediatrician, pediatric endocrinologist, obstetrician-gynecologist, otorhinolaryngologist, pediatric dentist, ophthalmologist, pediatric surgeon, pediatric urologist-andrologist, and traumatologist-orthopedist. According to data on somatometry (height and body weight indices), the level and harmony of physical development of schoolchildren were characterized due to WHO Growth Reference 2007 [11]. Physical development was defined as "average" if the adolescents' growth indicators fell within the interval Me±1SD of the scale of age-sex norms (Me — median; SD — standard deviation). Physical development was defined as "below average" if growth was less than –1.1 SD; "low" if it was less than –2.1 SD; «above average» if it was more than +1.1 SD; and "high" if it was more than +2.1 SD of Me±1 SD of the age-sex normative scale. The nutritional status of adolescents was assessed by Kettle's body mass index (BMI), which value was determined by dividing body mass (kg) by the square of body length (m2). Depending on the compliance of BMI values with the norms of the centile scale, schoolchildren were divided into groups:

- with harmonious physical development (15-85th percentile);

- with deficiency of body weight (5th to 15th percentile);
- with protein-energy malnutrition (below the 5th percentile);
- overweight (85th-95th percentile);
- obese (above the 95th percentile).

Statistical processing was performed with the program STATISTICA 7.0 (StatSoft, USA), using the χ^2 criterion modified by Pearson (with Yates correction). Differences in the results were considered statistically significant at $p < 0.05$.

The majority of examined schoolchildren had average physical development — 78.3±2.3% (80.1±2.9% of boys and 76.1±3.6% of girls). Above-average height was frequently observed in boys (11.7±2.3%) than in girls (4.3±1.4%; $p<0.05$); and high stature was observed only in boys (3.3±1.1%). Below-average physical development was observed more frequent in girls (19.6±3.3%) than in boys (8.3±1.9%; $p < 0.01$); short stature was found only in girls (2.2±1.2%). Harmonious body length and weight was observed in the majority of students — 60.4±2.7% (64.7±3.5% of boys and 58.7±4.1%). Disharmonious variants of physical development caused by deficiency of body weight were noted more often (21.7±2.3%) than those caused by excessive nutrition (17.9±2.4%). Body weight deficit was detected in 13.3±2.4% of boys and 17.4±3.2% of girls; a pronounced body weight deficit corresponding to protein-energy deficiency was registered in 6.7±1.8% of boys and 6.5±2.1% of girls. Overweight was determined in 10.0±2.2% of boys and 10.9±2.7% of girls; obesity was registered in 8.3±2.0% of boys and 6.5±2.1% of girls. Morbid obesity was detected in 13 adolescents (5.7±1.3%), who were recommended in-depth examination in specialized clinics.

Nowadays, the medical and social problems are still relevant: high prevalence of pathological conditions of the human body caused by low levels of iodine in the biosphere. Programs developed for iodine supplementation by salt iodization and iodine-containing preparations have not reached their goal in most regions of the country [12]. In examined students, endemic goiter was detected in 15.1±2.6% of boys and 45.6±4.2% of girls ($p < 0.001$). High prevalence of goiter in girls is consistent with menstrual dysfunction; different variants of menstrual disorders were found in 54.3±4.2% of schoolgirls, which required prescription of medical treatment. Girls were more likely than boys to have abundant acne (15.2±2.9% and 9.9±2.2%, respectively), which is consistent with the high prevalence of hirsutism and hypertrichosis caused by iodine deficiency in Chechen schoolgirls [13].

Both defects in oral care, dietary habits and quality of drinking water play a significant role in the development of dental caries. We noted a high prevalence of dental lesions: enamel defects and caries were detected in 65.1±3.5% of boys and 65.2±4.1% of girls. During the examination of oral cavity, the schoolchildren were shown the ways of effective dental care.

Orthopedic pathology was revealed in 43,7±3,5% of boys and 36,9±4,1% of girls. Different variants of posture disorders were noted in 36.7±3.4% of boys and 26.1±3.7% of girls ($p < 0.05$); flat foot — in 10.9±2.7% of girls and 6.7±1.8% of boys. Chest deformities requiring surgical correction (pigeon and funnel) were detected in 6 adolescents. Reduced visual acuity was demonstrated less frequently in boys (21.7±3.0%) than in girls (47.8±4.2%; $p < 0.001$). Most of the schoolchildren were referred for additional examination to an outpatient clinic to verify the diagnosis.

High prevalence of otorhinolaryngological pathology was revealed: in boys, chronic tonsillitis was found in 38.3±3.6%, nasal septum deviation — in 36.7±3.5%; in girls, the results were 34.8±4.1% and 26.1±3.7% ($p < 0.05$), respectively. Vasomotor rhinitis was noted in 9 schoolchildren, and one boy had a significant hearing loss. Changes in the cardiovascular system (autonomic dysfunction syndromes, heart murmurs, increased blood pressure) were noted in 10.0±2.2% of boys and 15.2±2.9% of girls. Diseases of gastrointestinal tract (gastric and duodenal ulcer, gastroesophageal reflux disease, irritable bowel syndrome) were in 6.3±1.3% of schoolchildren. According to the preventive examination data, group II of health was determined in 66.6±3.4% of boys and 65.2±4.1% of girls; group III — in 33.4±3.4% and 34.8±4.1%, respectively.

Thus, objective data on health status of schoolchildren and general morbidity rates can be assessed during mass preventive medical examinations of minors. The analysis of the obtained data makes it possible to plan measures for further examination, treatment, rehabilitation and follow-up monitoring of students in the Shaliskij district of the Republic of Chechnya.

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.

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ASSESSMENT OF THE LINEAR GROWTH OF PRESCHOOL BOYS IN ST. PETERSBURG

© Fatima K. Makoeva[1], Fatima U. Kozyreva[2], Inga Sh. Tuaeva[3]

[1] National State University of Physical Culture, Sports and Health named after P.F. Lesgaft. Decembrists st., 35, Saint Petersburg, Russian Federation, 190121
[2] Pirogov Russian National Research Medical University. Ostrovityanova st., 1, Moscow, Russian Federation, 117997
[3] North Ossetian State Medical Academy. Pushkinskaya st., 40, Vladikavkaz, Republic of Chechnya, Russian Federation, 362019

Contact information:
Fatima K. Makoeva — Candidate of Medical Sciences, Associate Professor, Department of preventive medicine and fundamentals of health. E-mail: fatima1510@yandex.ru ORCID: 0000-0002-0844-1703

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Abstract. The accelerated pace of the physical development of children during the period of the "half-height leap", which often coincides with the beginning of systematic schooling for boys, is accompanied by a decrease in the body's resistance to physical stress. In order to determine the features of the linear growth of boys before starting school, 1829 preschoolers were examined in the preparatory groups of educational institutions in various districts of St. Petersburg. The survey included somatometry, assessment of indicators according to the standards of the "WHO Growth Reference, 2007"; determination of the direction of growth processes according to the Verweck–Vorontsov index. Statistical analysis of the research materials was carried out by the methods of variation statistics using the STATISTICA 10.0 (StatSoft, USA) program. It was found that in 67.4% of the examined, the body length corresponds to the average values of the WHO standards. The level of physical development above the average was more common (24.3%) than the options due to low growth (8.3%). In 7.6% of preschool boys, a predominance of the intensity of "stretching" in height over an increase in height in width was noted, which makes it possible to classify them as a risk group for a decrease in endurance to physical exertion. The results of the study can be used as regional guidelines for individual dosing of physical activity in physical education classes at school and in sports sections for children.

Key words: *children; preschoolers; boys; physical development*

ОЦЕНКА ЛИНЕЙНОГО РОСТА МАЛЬЧИКОВ ДОШКОЛЬНОГО ВОЗРАСТА г. САНКТ-ПЕТЕРБУРГА

© Фатима Константиновна Макоева[1], Фатима Увжикоевна Козырева[2], Инга Шамильевна Туаева[3]

[1] Национальный государственный университет физической культуры, спорта и здоровья имени П.Ф. Лесгафта. 190121, г. Санкт-Петербург, ул. Декабристов, 35
[2] Российский национальный исследовательский университет им. Н.И. Пирогова. 117997, г. Москва, ул. Островитянова, 1
[3] Северо-Осетинская государственная медицинская академия. 362019, г. Владикавказ, ул. Пушкинская, 40

Контактная информация:
Фатима Константиновна Макоева — к.м.н., доцент, доцент кафедры профилактической медицины и основ здоровья. E-mail: fatima1510@yandex.ru ORCID: 0000-0002-0844-1703

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Резюме. Ускоренные темпы физического развития детей в период «полуростового скачка», который часто совпадает у мальчиков с началом систематического обучения в школе, сопровождается снижением резистентности организма к физическим нагрузкам. С целью определить особенности линейного роста мальчиков перед началом обучения в школе обследовано 1829 дошкольников в подготовительных группах образовательных учреждений в различных районах г. Санкт-Петербурга. Обследование включало соматометрию, оценку показателей по нормативам WHO Growth Reference 2007; определение направленности ростовых процессов по индексу Вервека–Воронцова. Статистический анализ материалов исследования проведен методами вариационной статистики с помощью программы STATISTICA 10.0 (StatSoft, USA). Выявлено, что у 67,4% обследованных длина тела соответствует средним значениям нормативов ВОЗ. Уровень физического развития выше

среднего встречался чаще (24,3%), чем варианты, обусловленные низким ростом (8,3%). У 7,6% мальчиков-дошкольников отмечено преобладание интенсивности «вытягивания» в высоту над увеличением роста в ширину, что позволяет отнести их к группе риска по снижению выносливости к физическим нагрузкам. Результаты исследования могут быть использованы в качестве региональных ориентиров при индивидуальном дозировании физических нагрузок на уроках физкультуры в школе и занятиях детей в спортивных секциях.

***Ключевые слова**: дети; дошкольники; мальчики; физическое развитие*

INTRODUCTION

Age-related dynamics of body length — linear growth — is one of the objective criteria of health and implementation of the genetic program of the development of a child. A growth of children in length is influenced by numerous endogenous and exogenous factors [1–5]. The complex of endogenous factors affecting development of child is individual, but the specificity of the impact of environmental factors is generalized and largely available for correction [6–10]. Minimizing the adverse effects of global external factors, such as the environmental situation, social and economic status, and others, requires a solution at the state level, but nutritional rationalization, correction of macro- and micronutrient imbalances, and optimization of physical activity are quite realizable at the individual level [11, 12]. Most children at the age of 6–7 years have an acceleration of growth processes, which requires from the child's organism a significant strain and reduces endurance to additional loads, for example, the beginning of systematic schooling is really important [13–15]. Monitoring of regional features of linear growth of preschoolers allows us to develop recommendations on the dosage of physical loads in physical education classes at school and sports sections for first-graders [16–18].

AIM

To identify the features of linear growth of boys in St. Petersburg during the preschool period.

MATERIALS AND METHODS OF THE STUDY

A total of 1829 boys attending preschool groups of children's educational institutions in St. Petersburg participated in the study by random sampling. Preschoolers were divided into groups: 1st (n=99) — boys at the age of 6 years; 2nd (n=490) — at the age of 6.5 years; 3rd (n=1149) — at the age of 7 years and 4th group (n=91) — at the age of 7.5 years. To examine the boys, in accordance with the ethical principles laid down in the Declaration of Helsinki, voluntary informed consent was signed by legal representatives of each child. When creating the electronic database, the initial data were depersonalized.

Physical development (PD) of preschoolers was assessed by means of comparative analysis of children's body length (BL) with WHO norms — WHO Growth Reference, 2007 [19]. Depending on the number of standard deviations (SD) that distinguish the child's BL value from the median (Me) of the age-sex scale, the following variants of PD were identified: "average" (AFD; ±1SD); "above average" (AAFD; from +1.1SD to +2SD); "high" (HFD; more than +2.1SD); "below average" (BAFD; from –1.1SD to –2SD); and "low" (LFD; less than –2.1SD). Within each age group, arithmetic mean (M), standard error of the mean (m), 95% confidence interval (95% CI), and median (Me) values were calculated for BL. The prevalence of the directionality of growth processes was determined using the "stenia" index created by Verveck and Vorontsov (SI). SI was calculated by dividing body length (cm) by the sum of chest circumference (cm) and doubled body weight (kg) [20]. Depending on the value of SI, we distinguished predominance of height growth (dolichomorphia and moderate dolichomorphia), harmonious FD (mesomorphia), and predominance of volumetric growth (brachymorphia and pronounced brachymorphia).

Statistical analysis of the data was performed by methods of variation statistics using STATISTICA 10.0 program (StatSoft, USA). Data samples were tested for normality of distribution using the Kolmogorov-Smirnov criterion. The results of the study are presented as P [95% CI] %, where P is the percentage, CI is the 95% confidence interval for the percentage. The statistical significance of differences between the indicators was analyzed using Pearson's χ^2 criterion (with Yates' correction). Differences in the results were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Characteristics of the level of physical development of preschoolers is presented in Table 1. The majority of boys in all age groups have average physical development (57.1–68.6%). In group 4, the number of children with AFD is less than in other groups, and the difference of indicators with group 3 is statistically significant (p=0.025). In all groups, above-average BL was more often recorded than low BL. Above average FD was almost equally recorded in all age groups (18.0–20.9%);

and higher boys were identified in Group 1 than in other groups. The difference in rates with Group 4 was statistically significant (p=0.042). More preschoolers with below average FD were in group 4 than in groups 3 (p<0.001), 2 (p=0.001) and 1. Stunting was detected in 26 children (1.5%), the prevalence rate was statistically significant only in Group 3 among all variants of FD.

According to the biological pattern, BL increased with age; the calculated group BL values are shown in Table 2. The BL gains were 3.4 cm from 6 to 6.5 years, 2.9 cm from 6.5 to 7 years and 2.1 cm from 7 to 7.5 years. The difference between groups was statistically significant (from p <0.01 to p <0.001). In all groups, the median values of WHO norms (Child Growth Standards, 2006) are higher than in the preschoolers examined by us.

The distribution of preschoolers according to the "stenia" index is shown in Table 3. According to I.M. Vorontsov, the coincidence of the beginning of systematic education and the phase of intensive linear growth may cause a decrease in physical and mental endurance in children. The majority of preschoolers had harmonious FD (mesomorphia); there were fewer such boys at the age of 6 years than in other groups, and in comparison with Group 3, the difference was statistically significant (p=0.022). In all groups there were more children with predominance of the processes of "stretching" in height over the increase in girth and latitudinal dimensions. Among six-year-old boys there were more children with moderate dolichomorphia than in groups 2 (p <0.001), 3 (p=0.005) and 4, which may indicate the start of their "half-height" growth spurt. Dolichomorphia, indicating a pronounced "stretching", was determined in 13 preschoolers (0.8%); the prevalence of dolichomorphia depending on age was not statistically significant. There were 22 boys with predominance of volumetric growth, 17 of them were in Group 3; age-dependent prevalence rates were also not statistically significant.

Table1. Characteristics of physical development of preschoolers (% [95% CI])

Таблица 1. Характеристика уровня физического развития дошкольников (%[95% ДИ])

Physical development / Физическое развитие	Age / Возраст					Note / Примечание
	6 years n=99 / 6 лет n=99	6,5 years n=490 6,5 лет n=490	7 years n=1149 / 7 лет n=1149	7,5 years n=91 / 7,5 лет n=91	Total / n=1829	
Low / Низкое	2,0 [0,6–3,4]	0,8 [0–1,6]	1,6 [1,2–2,0]	2,2 [0,8–3,6]	1,5 [1,2–1,8]	–
Below average / Ниже среднего	5,0 [2,8–7,2]	6,9 [5,8–8,08]	6,2 [5,5–6,9]	17,6 [13,7–21,5]	6,7 [6,1–7,3]	P_{2-4} <0,001 P_{3-4}<0,001
Average / Среднее	65,8 [61,1–70,5]	67,0 [64,9–69,1]	68,6 [66,5–70,7]	57,1 [52,0–62,2]	67,5 [66,4–68,6]	P_{3-4}=0,025
Above average / Выше среднего	18,2 [14,3–22,1]	19,6 [17,8–21,4]	18,0 [16,9–19,1]	20,9 [16,7–25,1]	18,6 [17,7–19,5]	–
High / Высокое	9,0 [6,1–11,9]	5,7 [6,7–6,7]	5,6 [4,9–6,3]	2,2 [0,8–3,6]	5,7 [5,2–6,2]	P_{1-4}=0,042

Table 2. Dynamics of body length in preschoolers

Таблица 2. Динамика длины тела у дошкольников

Indicator / Показатели	Age / Возраст			
	6 years n=99 / 6 лет n=99	6,5 years n=490 6,5 лет n=490	7 years n=1149 / 7 лет n=1149	7,5 years n=91 / 7,5 лет n=91
M (см)	117,5	120,9	123,8	125,9
m	0,52	0,24	0,16	0,67
95% ДИ / 95% CI	116,4–118,5	120,5–121,4	123,6–124,2	124,5–127,2
Me (см)	117,0	121,0	124,0	126,0
MeWHO (см)	116,0	118,4	121,7	124,5

Note: The difference in mean body length (M) was statistically significant between groups 1 and 2 (p <0.001); 2 and 3 (p <0.001); 3 and 4 (p <0.001).

Примечание: разница средних показателей длины тела (M) статистически значима между 1-й и 2-й (p<0,001); 2-й и 3-й (p <0,001); 3-й и 4-й (p <0,001) группами.

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Table 3. Value of "stenia" index of preschoolers (% [95% CI])

Таблица 3. Показатели индекса «стении» у дошкольников (%[95% ДИ])

Physical development / Физическое развитие	Age / Возраст					Note / Примечание
	6 years n=99 / 6 лет n=99	6,5 years n=490 6,5 лет n=490	7 years n=1149 / 7 лет n=1149	7,5 years n=91 / 7,5 лет n=91	Total / n=1829	
Pronounced brahimorfia / Выраженная брахиморфия	–	–	0,1 [0–0,2]	–	0,1 [0–0,2]	–
Brahimorfia / Брахиморфия	–	1,1 [0,6–1,6]	1,5 [1,1–1,9]	–	1,2 [0,9–1,5]	–
Mesomorphia / Мезоморфия	83,3 [79,5–87,1]	90,2 [88,9–91,5]	90,8 [89,9–91,7]	92,1 [89,2–95,0]	90,3 [88,1–92,5]	P_{1-3}=0,023
Moderate dolihomorfia / Умеренная долихоморфия	15,5 [11,7–19,3]	7,0 [5,8–8,2]	7,3 [6,5–8,1]	6,6 [3,8–9,4]	7,6 [7,0–8,2]	P_{1-2} <0,001 P_{1-3}=0,005
Dolihomorfia / Долихоморфия	1,2 [0,1–2,3]	1,7 [1,1–2,3]	0,3 [0,1–0,5]	1,3 [0,1–2,5]	0,8 [0,6–1,0]	P_{2-3}=0,022

CONCLUSION

The results of our study show the peculiarities of linear growth of metropolitan boys during the period of children's preparation for systematic schooling. We made the following conclusions based on the obtained data.

1. In 67.4% of the examined preschoolers the body length corresponds to the average values of WHO Growth Reference 2007.
2. The level of physical development above average was more frequent in children (24.3%) than variants caused by low growth (8.3%).
3. Median body length values in all age groups exceeded the WHO standards (WHO Growth Reference 2007). Standards developed by WHO (WHO Growth Reference 2007), which should be taken into account in the individual characterization of physical development of preschoolers living in St. Petersburg.
4. In 7.6% of preschool boys there was a predominance of linear growth intensity over growth in width, which allows us to assign them to the risk group of a possible decrease in the level of endurance to both physical and mental load. This circumstance should be taken into account when determining the physical education group for physical education classes at school and the intensity of training in sports sections.

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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COMPARATIVE ASSESSMENT OF THE PHYSICAL DEVELOPMENT OF BOYS AND GIRLS OF TAJIKISTAN

© Bibisoro I. Komilova, Nasimzhon S. Fozilov

North-Western State Medical University named after I.I. Mechnikov. Piskarevskiy pr. 47, Saint Petersburg, Russian Federation, 195067

Contact information:
Bibisoro I. Komilova — Clinical Resident, Department of Pediatrics and Pediatric Cardiology.
E-mail: bibisoro.komilova0404@gmail.com ORCID: 0000-0003-1124-015X

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Abstract. *Introduction*. Student youth is the most socially active and mobile group, which significantly determines the strategy and future of the country**.** *Purpose of research.* To evaluate the anthropometric indicators of the physical development of students in Tajikistan and compare them with the results of similar studies. *Material and methods.* We studied 390 students of the Khatlon State Medical University (KhSMU) of Tajikistan, among which there were 279 boys (71.5%), girls — 111 (28.5%), the average age was 19.3±1,7 years. The research program included the measurement of the main indicators of physical status: height (cm), body weight — BW (kg), body mass index — BMI (kg/m^2), right hand dynamometry (kg), somatotype determination. The results obtained were compared with data from similar studies of 15,686 students from 22 countries, whose average age was 20.8±2.6 years (Peitzer K. et al., 2014). *Results*. Average indicators of BMI, height and weight of students of KhSMU were 21.6±0.14 kg/m^2, 168.8±0.4 cm and 61.5±0.5 kg, respectively, while the same indicators of BMI, height and the weight of a similar group of young people from other countries were equal to: BMI from 18.1±1.9 kg/m^2 to 25.4±4.5 kg/m^2; height — from 163±0.07 m to 178±0.07 m, weight — from 56.7±7.8 kg to 78.0±13.9 kg, respectively. According to comparing, it was found that there were more students with normal weight in KhSMU than the average among girls and boys from other countries of the world, among the girls more than 15.4% and more than 19.1% among the boys. Body weight deficiency among girls of KhSMU was detected 6.8% less and indicators of overweight and obesity in girls from other countries were on average 7.6% more often than girls in KSMU. To assess the significance of differences was used Student's t-test, they were considered reliable at a significance level $p < 0.05$. *Conclusion.* It was revealed that the indicators of the physical development of boys and girls in Tajikistan in terms of weight and height parameters differed from those of their peers from other countries, which may be an indicator of the socio-economic characteristics of living.

Key words: *physical development; anthropometry; somatometry; dynamometry; indices; boys and girls*

СРАВНИТЕЛЬНАЯ ОЦЕНКА ФИЗИЧЕСКОГО РАЗВИТИЯ ЮНОШЕЙ И ДЕВУШЕК ТАДЖИКИСТАНА

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Северо-Западный государственный медицинский университет им. И.И. Мечникова. 195067, г. Санкт-Петербург, Пискаревский пр., 47

Контактная информация:
Бибисоро Икромиддиновна Комилова — клинический ординатор кафедры педиатрии и детской кардиологии.
E-mail: bibisoro.komilova0404@gmail.com ORCID: 0000-0003-1124-015X

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Резюме. *Введение.* Студенческая молодежь является наиболее социально активной и мобильной группой, которая в значительной мере определяет стратегию и будущее государства. *Цель исследования* — оценить антропометрические показатели физического развития студентов Таджикистана и сравнить их с результатами подобных исследований. *Материалы и методы.* Обследовано 390 студентов Хатлонского государ-

ственного медицинского университета (ХГМУ) Таджикистана, среди которых юношей было 279 (71,5%), девушек — 111 (28,5%); средний возраст составлял 19,3±1,7 года. Программа исследований включала измерение основных показателей физического статуса: рост (см), масса тела — МТ (кг), индекс массы тела — ИМТ (кг/м^2), динамометрия правой кисти (кг), определение соматотипа. Полученные результаты сравнили с данными подобных исследований 15 686 студентов из 22 стран мира, средний возраст которых составлял 20,8±2,6 лет. *Результаты.* Средние показатели ИМТ, роста и массы тела студентов ХГМУ составили 21,6±0,14 кг/м^2, 168,8±0,4 см и 61,5±0,5 кг соответственно, в то время как такие же показатели ИМТ, роста и массы тела аналогичной группы молодежи из других стран составляли: ИМТ от 18,1±1,9 кг/м^2 до 25,4±4,5 кг/м^2; рост — от 163±0,07 см до 178±0,07 см, масса тела — от 56,7±7,8 кг до 78,0±13,9 кг соответственно. При сравнении установлено, что студентов с нормальной массой тела было больше на 15,4% среди девушек ХГМУ, а среди юношей — на 19,1%, чем в среднем среди девушек и юношей других стран мира. Показатели дефицита массы тела у девушек ХГМУ были на 6,8% меньше, чем у девушек других стран. Одновременно показатели избыточной массы тела и ожирения у девушек других стран были больше на 7,6% по сравнению с девушками ХГМУ. При определении достоверности различий использовали t-критерий Стьюдента, считали его достоверным при уровне значимости p <0,05. *Заключение.* Выявлено, что показатели физического развития юношей и девушек Таджикистана по весо-ростовым параметрам отличались от таковых у сверстников из других стран, что может быть индикатором социально-экономических особенностей проживания.

Ключевые слова: *физическое развитие; антропометрия; соматометрия; динамометрия; индексы; юноши и девушки*

INTRODUCTION

Students (boys and girls), united by specific conditions of education and lifestyle, constitute a special social group. Their physical health is a feature that determines the level of public health. Studying in higher education is a specific form of intellectual activity, which leads to changes in lifestyle, affects health, requires the development of adaptive properties of a human body, reliability of its physical and mental state. The impact of educational loads, intensification of the educational process, increased requirements to the volume and quality of knowledge, as well as violation of the motor regime negatively affects the functional capabilities of the students' organism. This leads to a decrease in adaptation reserves, situation of inconsistency of regulation mechanisms of autonomic functions, which are manifested in the form of impairment of performance, increased fatigue of students [2–4].

In the last two decades, physiologists, physicians, and educators have increased interest in studying the problem of correlation between the general, private, and local constitution of the human organism, which makes it possible to determine and predict the specificity of reactive processes occurring in any organ or organ system. The relationship between constitutional features and health is one of the most important aspects of researches in constitution [5].

Nowadays, to optimize physical education and health promotion of a person, an approach based on taking into account the peculiarities of physical constitution is used. At the same time, it is necessary to take into account that the constitutional belonging of a person is quite dynamic at the population level, depending on many factors (age, sex, ethnicity, environmental and other features), which requires constant revision of the somatic status of a person. Not the whole period of individual development is equally reflected from the standpoint of anatomical and anthropological science. According to the literature sources, there is a sufficient number of publications on physical development and features of somatotype in the period of newborn, in childhood and adolescence, in people of mature, elderly and old age [6]. To a lesser extent, attention is paid to adolescence, which is caused by intensive changes in body composition during this period, the need for "fractional" analysis of the considered indicators in the age aspect (no more than in the age of one or two years) [6, 7].

The anthropometrics for determining the level of physical development is extremely informative and allows to examine a large contingent in a short time, which makes it indispensable for population monitoring. The need for continuous monitoring of the younger generation in different regions can hardly be overestimated [8–10].

AIM

To evaluate anthropometric indicators of physical development of students in Tajikistan and compare our results with results of similar studies.

MATERIALS AND METHODS

Anthropometric measurements were performed in 390 students of Khatlon State Medical University (KSMU) of Tajikistan, among whom 279

(71.5%) were males and 111 (28.5%) were females. The age of students ranged from 17 to 26 years (mean age 19.3±1.7 years). At the same time, the predominant majority (96.4%) corresponded to the age group of 18–19 years. The anthropometric research program included measurement of the main indicators of physical status: height (cm), body weight — BW (kg), body mass index (BMI) (Kettle II index, kg/m^2), muscle strength of the leading arm (kg) and determination of somatotype.

Conducted anthropometric studies was done due to the requirements that ensure accuracy and enable comparison of the obtained results. The data on anthropometric measurement were entered into a spreadsheet, as well as into individual cards, which had certain rules of filling in to avoid errors in further processing of the obtained data.

Determination of height, body weight and dynamometry were performed according to the requirements known in propaedeutics. Body mass index (BMI, Kettle II index, kg/m2) was calculated according to the formula:

$$I = \frac{m}{h^2},$$

where I — BMI; m — body mass; h^2 — squared body length.

According to the World Health Organization (WHO) classification, the Kettle II index can be used to determine a person's weight category: normal — 18.5–24.9, deficit BW — less than 18.5–16, overweight — 25–30, obesity — 30–35 [3]. According to morphological constitutional classification, all students were categorized into normosthenic, hypersthenic and asthenic body types (methodology of M.V. Chernorutsky's was used). The obtained results were compared with the data of studies of 15 686 students from 22 countries of the world, the average age of whom was 20.8±2.6 years. One study was made by comparison based on the large-scale number of subjects and countries. This was the main factor for the legitimate use of this research work for comparison with our results.

Anthropometric method of research is the "gold standard" for assessing physical development, including overweight and obesity. This method was also applied in the studies of foreign scientists, which allowed us to compare the indicators [1, 9]. To compare individual anthropometric indicators of boys and girls, students from the following countries were selected: Tunisia, Jamaica, Philippines, Laos, Madagascar, Russia, in which the data had sharp or more significant differences in minimum and maximum indicators in relation to the compared group of students from Tajikistan.

To evaluate the results of the study, descriptive statistics was applied in the MS Excel application software package by calculating the main statistical indicators: for quantitative characteristics we calculated the mean (arithmetic) value (M), standard deviation (SD), standard error of the mean (SEM), for qualitative characteristics — frequency of occurrence (%). The Student's t-criterion was used to determine the reliability of differences; they were considered reliable at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

It was revealed that the average height of male students of Tajikistan was 172.5±0.51 cm, girls — 159.4±0.8 cm, and the average value of body mass index was 63.9±0.59 kg/m2 and 55.2±0.92 kg/m^2 respectively. In KSMU students, the individual value of the minimum of length was 148 cm and the maximum was 193 cm. The value of individual minimum and maximum of BW ranged from 38 kg to 113 kg. When BMI results were evaluated, the mean value in students was 21.6±0.14 kg/m^2, including 21.4±2.8 kg/m^2 in boys and 21.7±3.1 kg/m^2 in girls. The minimum and maximum BMI values ranged from 16.4 kg/m^2 to 36.2 kg/m^2. Normal length to weight ratio calculated by Kettle II index was observed in 319 (81.8%) students: 233 (83.5%) boys and 86 (77.5%) girls. It should be noted that 39 (10.0%) students were underweight: 27 (9.7%) males and 12 (10.8%) females. Overweight was detected in 27 (6.9%) students: 16 (5.7%) males and 11 (9.9%) females. Obesity was detected in 5 (1.3%) students: 3 (1.1%) boys and 2 (1.8%) girls.

When people were distributed by morphological constitutional types, it was found that the majority of students corresponded to the normosthenic type of physique 203 (52.1%), asthenic — 125 (32.0%) and hypersthenic — 62 (15.9%). It was revealed that the most frequent normosthenic somatotype was found in 140 (50.2%) boys and 63 (56.8%) girls; 90 (32.3%) and 35 (31.5%) students respectively had asthenic type of physique, 49 (17.5%) boys and 13 (11.7%) girls had somatotype defined as hypersthenic.

Dynamometric index of muscle strength in normosthenic young men was 72,1±1,95 kg, in girls — 31,0±2,5 kg; in asthenic young men — 66,07±2,44 kg, in girls — 30,1±3,95 kg; in hypersthenic young men the index of muscle strength was 75,6±3,3 kg, and in girls — 38,0±6,6 kg. The individual maximum of the index of muscle strength of the right hand in students of all somatotypes was: in boys — 92–95 kg, girls — 55–63 kg, the indi-

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vidual minimum — 35–38 kg in boys and 13–27 kg in girls.

The dependence of arm strength on the type of constitution was revealed as important regularity in analysis: arm strength in the general group of students of hypersthenic type is significantly greater (P_1 <0.001). In young men, this pattern is also present, except for an unreliable difference between the normosthenic and hypersthenic types (P_2 >0.05). In girls, a similar unreliable difference was found between asthenic and normosthenic type of constitution (P_1 >0.05) (Table 1).

As the result of our study, we obtained a complete picture of the degree of correspondence of students' BW to their height, as well as their quantitative representation in different constitutional groups, dynamometric indices of the leading hand depending on the type of constitution.

There were more boys with normal weight and height (83.5%) than girls (77.5%). It should be noted that BW deficiency as well as overweight and obesity were relatively more frequent in girls than in boys — 1.1 and 4.2%, respectively. Height was significantly higher in males (172.5±0.51 cm) than in females (159.4±0.8 cm). Also, obesity was more frequently detected in girls (1.8%) than in boys (1.1%). Total deviation from normal weight and height was more frequent in girls than in boys.

According to the data of foreign researchers, the average value of height and body mass indices in the population of a similar group of students was equal to 162.9±6.9 and 62.3±7.6, respectively. BMI averaged 22.3±3.6 kg/m^2. Normal BW values was observed in 62.1% of girls and 64.4% of boys, and BW deficiency was found in 17.6% of girls and 10.8% of boys. Excess BW was found in 14.1% of girls and 18.9% of boys, and obesity was found in 5.2% of girls and 5.8% of boys [8].

We found that the indicators of normal BW in female students of KSMU were 13.6% higher than in girls in other countries of the world during comparing the obtained data. The indicators of body mass deficiency in KSMU girls were 6.8% less than in girls in other countries. At the same time, the rates of overweight and obesity among girls in other countries were 7.6% higher compared to girls in KSMU (Fig. 1).

Indicators of normal BW in young men of KSMU students were 14.8% higher than those in young men in other countries of the world. The indicators of excess BW and obesity in young men of different countries were 17.9% higher than in young men of KSMU (Fig. 2).

Tables 2 and 3 present the indicators of physical development of students of countries of the world, in which the maximum and minimum indicators of physical development were found, in comparison with the data of our study.

According to the Table 3, Tajikistan's boys outperformed Laos and India in body length, but had lower results compared to boys from Russia, Tunisia and Pakistan. In terms of weight, boys of Tajikistan outperformed boys from Laos, India and Pakistan, but had a less levels to their peers from Russia and Tunisia. The BMI values of all young

Table 1. Indicators of dynamometry of muscle strength of the right hand (kg) in accordance to the somatotype

Таблица 1. Показатели динамометрии мышечной силы правой кисти (кг) в зависимости от соматотипа

Sex / Контингент	Somatotype / Конституциональный тип			Reliability (P) / Достоверность (P)
	asthenic arm strength, kg / астенический сила руки, кг	normosthenic arm strength, kg / нормостенический сила руки, кг	hyperstenic arm strength, kg / гиперстенический сила руки, кг	
Young men, n=279 / Юноши, n=279	66,1±2,44	72,1±1,95	75,6±3,30	P_1 <0,001 P_2 >0,05 P_3 <0,001
Young women, n=111 / Девушки, n=111	30,1±3,95	31,0±2,50	38,0±6,60	P_1 >0,05 P_2 <0,001 P_3 <0,001
All students, n=390 / Все студенты, n=390	56,0±0,44	59,3±0,33	67,8±0,62	P_1 <0,001 P_2 <0,001 P_3 <0,001

Note: P_1 — reliability of differences in arm strength between asthenic and normosthenic types; P_2 — reliability of differences in arm strength between normosthenic and hypersthenic types; P_3 —reliability of differences in arm strength between asthenic and hypersthenic types.

Примечание: P_1 — достоверность различий силы руки между астеническим и нормостеническим типами; P_2 — достоверность различий силы руки между нормостеническим и гиперстеническим типами; P_3 — достоверность различий силы руки между астеническим и гиперстеническим типами.

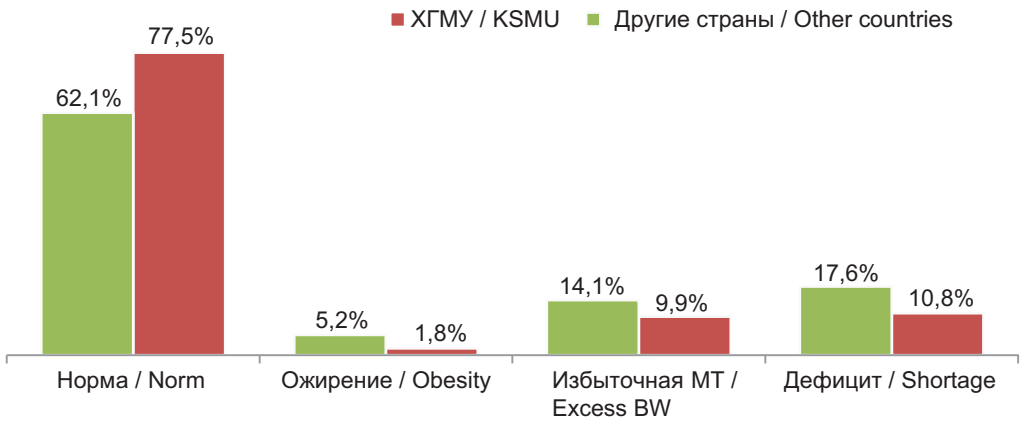

Рис. 1. Сравнительные показатели количества девушек по уровню ИМТ (%)

Fig. 1. Comparative indicators of girls number by the level of BMI (%)

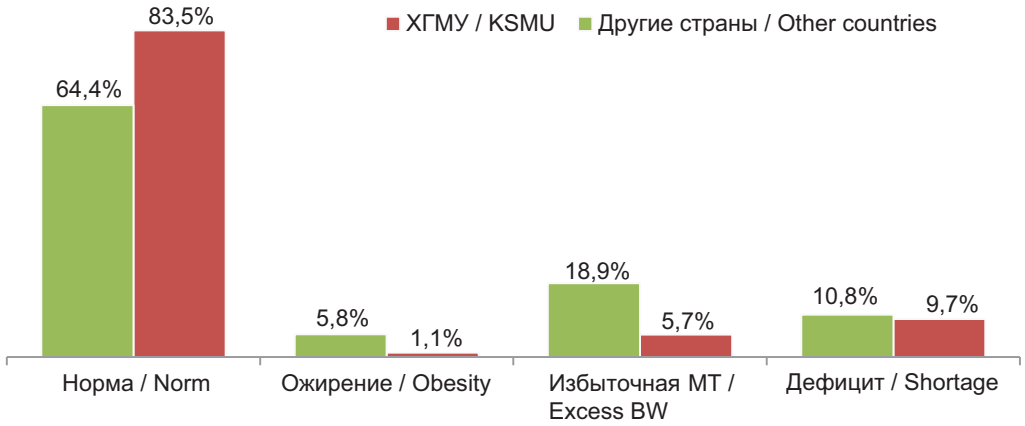

Рис. 2. Сравнительные показатели количества юношей по уровню ИМТ (%)

Fif. 2. Comparativeindicators of boysnumber by the level of BMI (%)

Table 2. Comparative indicators of the physical development of girls in some countries [9]

Таблица 2. Сравнительные показатели физического развития девушек некоторых стран [9]

Country / Страны	N / N	Age (SD) / Возраст (СО)	Height (SD), cm / Рост (СО), см	Body weight (SD), kg / Вес (СО), кг	BMI (SD), kg/m^2 / ИМТ (СО), кг/м^2	Deficiency of BW, % / Дефицит МТ, %	Normal BW, % / Норм. МТ, %	Over-weight, % / Избыток МТ, %	Obesity, % / Ожирение, %
Russia / Россия	404	19,8 (1,7)	167 (0,06)	57,3 (8,6)	20,5 (2,9)	24	69,3	5,9	0,7
Tunisia / Тунис	615	21,0 (1,7)	165 (0,06)	62,5 (9,9)	23,0 (3,6)	7,3	67,3	20,3	5
Jamaica / Ямайка	516	21,1 (4,9)	164 (0,09)	63,1 (15,3)	23,4 (5,6)	11,8	60,1	17,4	10,7
Philippines / Филиппины	573	18,3 (1,3)	154 (0,09)	49,3 (10,6)	20,6 (3,6)	27,1	54,3	14,1	4,5
Laos / Лаос	499	22,1 (1,9)	156 (0,06)	50,5 (8,8)	20,8 (3,6)	28,7	52,5	14,6	4,2
Madagascar / Мадагаскар	398	19,6 (1,5)	156 (0,06)	50,7 (7,7)	20,8 (2,8)	20,1	74,3	4,6	1
Tajikistan , Таджикистан	111	19,1 (1,1)	159,4 (0,8)	55,2 (0,9)	21,7 (3,1)	10,8	77,5	9,9	1,8

Note: SD — standard deviation (SD).

Примечание: СО — среднеквадратическое отклонение (SD).

men are also almost the same. Young men from Tajikistan have a slightly higher prevalence of BW deficiency than young men from Russia and Tunisia. Excess BW and obesity are significantly less common in Tajikistan than in the comparison group, with the exception of boys from Pakistan.

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Table 3. Comparative indicators of the physical development of boys in some countries [9]

Таблица 3. Сравнительные показатели физического развития юношей некоторых стран [9]

Country / Страны	N / N	Age (SD) / Возраст (СО)	Height (SD), cm / Рост (СО), см	Body weight (SD), kg / Вес (СО), кг	BMI (SD), kg/m^2 / ИМТ (СО), кг/м^2	Deficiency of BW, % / Дефицит МТ, %	Normal BW, % / Норм. МТ, %	Over-weight, % / Избыток МТ, %	Obesity, % / Ожирение, %
Russia / Россия	381	20,1 (1,9)	179 (0,09)	76,7 (11,0)	23,7 (3,3)	2,9	69	24,4	3,7
Tunisia / Тунис	295	23,7 (4,1)	178 (0,07)	74,8 (13,7)	23,7 (4,1)	4,1	67,1	23,4	5,4
Pakistan / Пакистан	319	20,2 (1,8)	177 (0,11)	57,0 (5,1)	18,1 (1,9)	61,1	36,7	2,2	0
Laos / Лаос	260	22,6 (1,8)	163 (0,07)	56,7 (7,8)	21,3 (2,8)	8,1	68,1	19,2	4,6
India / Индия	541	17,9 (0,6)	167 (0,09)	63,2 (11,9)	22,7 (4,5)	11,8	47,9	28,5	11,8
Tajikistan , Таджикистан	279	19,29 (0,06)	172,5 (0,5)	63,9 (0,59)	21,4 (2,8)	9,7	83,5	5,7	1,1

Note: SD — standard deviation (SD).

Примечание: СО — среднеквадратическое отклонение (SD).

It should be noted that, according to our data and available literature, in general, girls are more often have a deficiency of BW than boys. Explaining this phenomenon, we can assume that modern girls strive to conform to some "ideal" ideas about how they should look. Such a social phenomenon as fashion in this context can be considered as a rather powerful social factor that has a significant impact on gender features in the morphological transformation of modern youth [10].

At the same time, the comparative analysis shows that the indicators of physical development corresponding to age norms in young men and girls of KSMU are much higher than those of their peers from other countries of the world.

CONCLUSION

Thus, the study on measurement of the main anthropometric and dynamometric parameters revealed the facts characterizing the features of physical development of students of KSMU and some countries according to the data similar to our study. The obtained indicators, if necessary, can be used as norms in analyzing the physical development of young men and girls of the corresponding population at the regional level, which is important in preventive examinations and in many branches of practical medicine. It was found that the physical development indicators of young men and girls in Tajikistan differed in weight and height parameters from those of their peers from other countries, which may be an indicator of socio-economic characteristics of the territories of residence.

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.

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ORAL MICROBIOTA IN EARLY-CHILDHOOD CARIES PEDIATRIC PATIENTS — THE PILOT STUDY

© Elena A. Klimova, Natalia A. Sokolovich, Diana A. Kuzmina

Saint Petersburg State University, Faculty of Dentistry and Medical Technology. 21 Line V.O. 8a, Saint Petersburg, Russian Federation, 199106

Contact information:
Elena A. Klimova — Assistant of the Department of Dentistry. E-mail: doctor.klimova@yandex.ru ORCID: 0009-0007-1740-3294

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Abstract. Carious lesions continue to be an urgent problem of modern practical healthcare. On the territory of Russia, there is insufficient data from epidemiological studies among children under 3 years of age on the incidence of early childhood caries. In Western countries, patients with early childhood caries are treated without fail under general anesthesia with concomitant hospitalization, which is stressful for the child and family, as well as a costly method for healthcare. Modern metagenomics makes possible to study the fundamental aspects of the problem of the etiology of caries with the subsequent development of etiotropic therapy and means of prevention. Along with other microorganisms, the genus Streptococcus is the leader in the development of the carious process. The study of pathogens, as well as the function of specific genes in dental pathology, becomes possible with the help of metagenomic sequencing. In this paper, children with early childhood caries were studied by polymerase chain reaction followed by metagenomic sequencing. The spectrum of microorganisms in different children was studied and distributed among families. The study showed the need for further study of oral microbiota in children with early childhood caries to identify critically important pathogens.

Key words: *caries epidemiology; early childhood caries; metagenome; biofilm; caries*

МИКРОБИОТА ПОЛОСТИ РТА ПАЦИЕНТОВ ПРИ РАННЕМ ДЕТСКОМ КАРИЕСЕ — ПИЛОТНОЕ ИССЛЕДОВАНИЕ

© Елена Александровна Климова, Наталья Александровна Соколович, Диана Алексеевна Кузьмина

Санкт-Петербургский государственный университет, факультет стоматологии и медицинских технологий.
199106, г. Санкт-Петербург, 21-я линия В.О., 8а

Контактная информация:
Елена Александровна Климова — ассистент кафедры стоматологии. E-mail: doctor.klimova@yandex.ru
ORCID: 0009-0007-1740-3294

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Резюме. Кариозные поражения продолжают оставаться актуальной проблемой современного практического здравоохранения. По территории России недостаточно данных эпидемиологических исследований среди детей до 5 лет по заболеваемости кариесом раннего детского возраста. В западных странах пациентов с кариесом раннего детского возраста лечат в обязательном порядке в условиях общего обезболивания с сопутствующей госпитализацией, что является стрессом для ребенка и семьи, а также затратным методом для здравоохранения. Современная метагеномика дает возможность изучить фундаментальные аспекты проблемы этиологии кариеса с последующей разработкой этиотропной терапии и средств профилактики. Наряду с другими микроорганизмами по значению в развитии кариозного процесса лидирует род *Streptococcus*. Изучение патогенов, а также функции специфических генов при стоматологической патологии становится возможным при помощи метагеномного секвенирования. В настоящей работе исследован биологический материал с поверхности зубов детей с кариесом раннего детского возраста ме-

тодом полимеразно-цепной реакции с последующим метагеномным секвенированием. Спектр микроорганизмов был изучен и распределен по семействам. Исследование показало необходимость дальнейшего изучения микробиоты у детей с ранним детским кариесом для выявления критически значимых патогенов и разработки специальных средств профилактики, персонализированных данному возрасту.

Ключевые слова: *эпидемиология кариеса; ранний детский кариес; метагеном; биопленки; кариес*

THE RELEVANCE OF THE PROBLEM

Early childhood caries (ECC) is a medical and social problem that seriously affects child health and the quality of life of children and their families. According to the World Health Organization, about 620 million children in the world suffer from this disease. ECC is classified as caries occurring in children younger than 72 months old, with the first signs of the disease manifesting between 18 and 24 months old.

In the scientific literature, early childhood caries (ECC) in children 3–5 years old is defined as one or more carious (C), cariesogenic missing (CM), or sealed (S) temporary anterior teeth or amount of CCMS surfaces more than 4 (at the age of 3 years), more than 5 (at the age of 4 years), or more than 6 (at the age of 5 years).

According to the literature, 7% of children under 3 years old in developed European countries have early childhood caries. In developing countries this indicator reaches 35%. The prevalence of dental caries in children under 3 years old in Moscow reaches 57%? according to L.P. Kiselnikova (2013),. There is no data from epidemiological studies among this age group in Russia.

In Western countries, patients with early childhood caries are treated under general anaesthesia with concomitant hospitalisation. This method is often psychologically stressful for the child and his family. It is also a very expensive method for the health care system. In addition, the statistics of caries recurrences in the next 2 years after ECC sanitation demonstrates a disappointing result. In our opinion, this disease requires a comprehensive study and development of special personalised methods of prevention before the onset of pathology, as well as after complete sanation.

THE FUNDAMENTAL RATIONALE OF THE RESEARCH

Metagenomics provides an opportunity to study the fundamental aspects of the problem of caries etiology with the subsequent development of etiotropic therapy and means of prevention. Along with other microorganisms, the Streptococcus leads in terms of importance in the development of the carious process. The study of pathogens, as well as the function of specific genes in dental pathology becomes possible with the help of metagenomic sequencing.

Oral diseases, including periodontal diseases and dental caries, occupy leading positions in terms of prevalence among human infectious diseases [2]. Caries continues to be an urgent problem in medicine in all regions. Its destructive effect leads to significant expenses in the health care system [3].

The human oral cavity is a moist, warm environment which can be easily colonised by micro-organisms. The presence of both hard and soft tissues, each with a complex microanatomy, favours the creation of many different niches and supports the existence of a diverse microbiota. It is now known that the most common oral diseases, the dental caries and its complications, are likely to be caused by multispecies communities rather than by single, isolated pathogens [1]. Different microbial species coexist and form a polymicrobial biofilm, the plaque in the oral cavity [2, 6].

Metagenomics using next generation sequencing (NGS) technology reproduces bacterial composition and genomic profiles of bacteria to study the relationships between microbial diversity, genetic variations and oral diseases. According to Richard J. Lamont, the study of the genome of oral microorganisms is at an early stage of development [6]. The roles of pathogenic species and the function of specific genes in the development of dental disease have been discovered by metagenomic analysis. Annotations of oral microbial genomes support the hypothesis of association of specific genes or metabolic pathways with oral health and specific diseases [6]. Scientists have also proposed a model of three-level interactions occurring in the microbiome and determining the state of dental health or disease [2].

Streptococcus are the microorganisms with the most important relationship to pathological processes. These microbes are often the first surface colonisers and numerically dominant in the human oral cavity. A large number of interactions between *Streptococcus* and other bacteria have been documented and suggest their critical importance in the development of multispecies mi-

crobial communities and for the transition from dental health to disease states.

Streptococcus are Gram-positive facultative anaerobic cocci. Improvements in microscopy techniques and biofilm models allow a detailed view of the spatial distribution of Streptococcus in oral biofilm. There has been an increase in the use of methods to analyse specific genes that modulate interspecies interactions. A number of studies have also found that Streptococcus produce a spectrum of extracellular factors that facilitate their integration into multi-species communities and enable them to form "social networks" with their "neighbouring" species. These "community integration factors" include adhesins and receptors that promote aggregation and small signalling molecules.

Bishop et al. (2009) identified 4 groups of oral *Streptococcus* (Figure 1) [1]. Two species of Streptococcus group *Mutans*, named *S. mutans* and *S. sobrinus*, were found to be associated with human dental caries. Their acid-producing properties and the potential of being able to exist in an acidic environment are directly related to the cariesogenic potential of these bacteria. In order to survive in the acidic conditions of the human oral cavity with hundreds of competing bacteria, both species have evolved many adaptation mechanisms [4].

The cariesogenic potential of *S. mutans* may be due to multiple virulence factors. These factors are: 1) the ability to metabolise carbohydrates with concomitant release of lactic acid (acid generation); 2) the tolerance to and ability to survive in an acidic environment; 3) the ability to facilitate hydroxyapatite binding and promote intercellular adhesion; 4) the formation of multi-bacterial grouped structures in dental plaque (biofilm formation); and 5) the successful elimination of other bacterial strains through the production of bacteriocins. The biofilm enters a state of progressive cariesogenic potential when these virulence factors of *S. mutans* and other micro-organisms are expressed phenotypically and work together [9].

Molecular studies have shown that *S. mutans* is not always present in caries. Other acid-producing bacteria may also play a role in the pathogenesis of dental caries in some individuals are *Lactobacillus* spp., *Bifidobacterium dentium, S. sobrinus, S. salivarius/S. vestibularis* and *S. parasanguinis* [7–9].

If *S. mutans* is involved, the additional presence of the bifidobacterium *Scardovia wiggsiae* correlates closely with dental caries [5].

The quantitative prevalence of primary colonisers *S. gordonii* and *S. sanguinus* in the oral cavity contributes to limiting the growth of *S. mutans* [7, 8]. The availability of oxygen to *S. gordonii* and *S. sanguinus* and their production of hydrogen peroxide allow these microorganisms to compete effectively with other streptococcal species, including *S. mutans* [7–9]. In contrast, *S. mutans* can antagonise the growth of other oral *Streptococcus* by the formation and release of bacteriocins [7, 8]. Interspecies antagonism, similar to other environmental factors in the oral cavity, helps to determine the outcome of the competitive struggle between *Streptococcus* which is primary colonising the oral cavity and *S. mutans*. Ultimately, the patient's dental health status is shaped or diseases being diagnosed, including dental caries.

MATERIALS AND METHODS

Six children 20–36 months old with no concomitant general pathology, with an unremarkable allergological anamnesis and who had not previously used antibacterial therapy were under observation for 3 months. The children underwent a complete dental examination and the need for routine sanation under general anaesthesia was identified. The patients were divided into two groups according to gender.

Group 1 — 3 female patients on mixed feeding.

Group 2 — 3 male patients on mixed feeding.

The selection criteria was presence of nocturnal breastfeeding and sugar in the diet, when patients were involved in the groups. Patients were subjected to bacteriological and molecular biological tests by polymerase chain reaction (PCR) with real-time fluorescence detection of amplification results before sanitation.

Material used for bacteriological examination was collected from the surfaces of the first temporary molars of the mandible and incisors of the maxilla without special hygienic treatment. The material was taken in the morning, before the brushing procedure, using a sterile paper endodontic pin of standard size (No. 30) and disposable sterile polypropylene probes with synthetic pile, which were then placed in the solution "DNA Express" for subsequent transport. The system was kept at 2–4 °C until transport. Then samples were transferred to the laboratory in a refrigerated state for 1 hour. Bacteriological examination was performed according to the generally accepted rules of clinical anaerobic microbiology.

The samples were then subjected to high-throughput metagenomic sequencing at the SPbSU Resource Centre using an Ion Torrent PGM

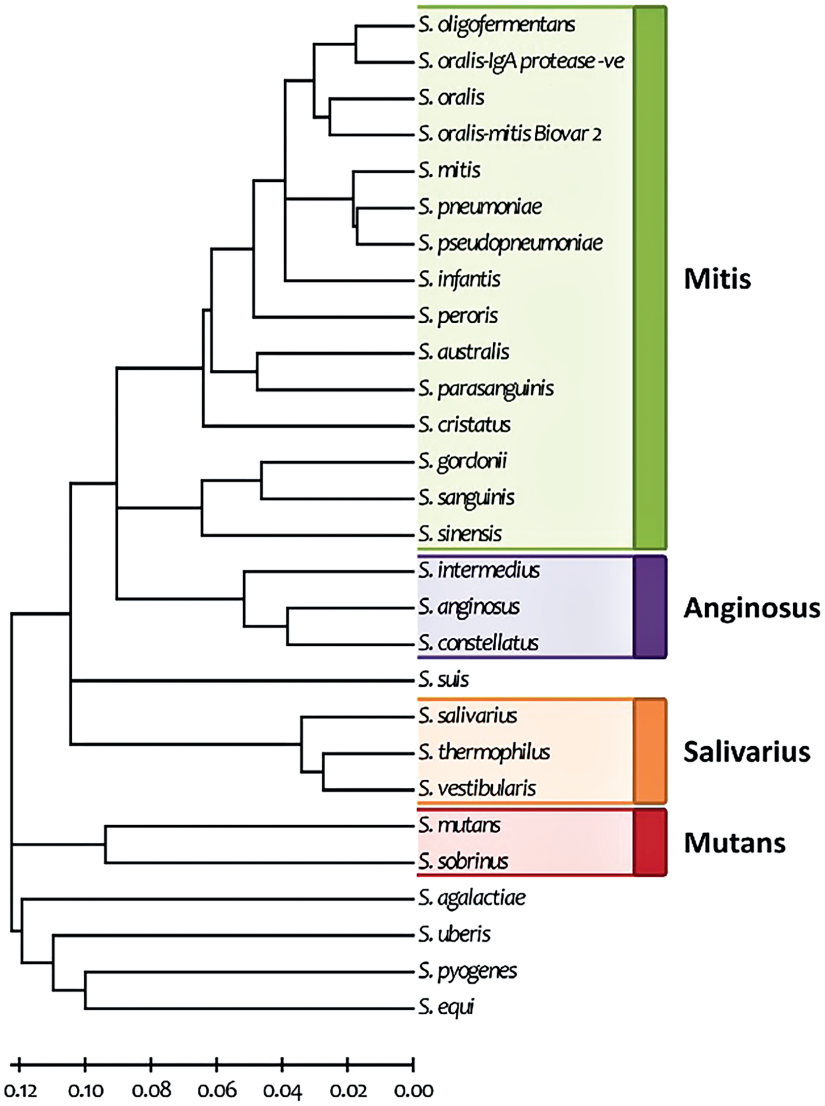

Fig. 1. Phylogenetic tree of the genus Streptococcus (according to Bishop et al., 2009)
Рис. 1. Филогенетическое древо рода *Streptococcus* (по Bishop et al., 2009)

sequencer (Life Technologies) for 16S RNA marker genes using "universal" primers to identify the microbial community.

CONCLUSIONS

Plaque samples obtained from the teeth of 1st group showed a higher number of opportunistic and cariesogenic microflora in contrast to samples from group 2. Due to the high cost of the study, these results need quantitative support and future confirmation or refutation. In our opinion, they are worthy of discussion in the professional community on the basis of the significance of this pathology in terms of the proportion of ECC among dental diseases of children.

The next step is to study the changes in the microbiota during 6–18 months after sanitation to draw preliminary conclusions on the materials used. The other step is to change the composition of child's microbiota under conditions of complete sanitation. This publication also aims to encourage paediatric dentists to actively participate in research on ECC.

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 the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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PATHOLOGY OF THE ORAL CAVITY IN CHILDREN WITH DIABETES MELLITUS

© Lyudmila N. Soldatova[1, 2], Andrey K. Iordanishvili[1, 3], Anastasiia V. Fedorova[1, 4]

[1] Military Medical Academy named after S.M. Kirov. Akademician Lebedeva st., 6, Saint Petersburg, Russian Federation, 194044
[2] Pavlov First Saint Petersburg State Medical University. Ul. L'va Tolstogo, 6–8, Saint Petersburg, Russian Federation, 197022
[3] Saint Petersburg Medico-Social Institute. Kondratyevsky pr., 72, lit. A, Saint Petersburg, Russian Federation, 195271
[4] Medved LLC clinic. Rostovskaya st., 17/4 A, Saint Petersburg, v. Shushura, Russian Federation, 196634

Contact information:
Lyudmila N. Soldatova — Doctor of Medical Sciences, Associate professor, professor of dentistry of children's age and orthodontics department Pavlov First Saint Petersburg State Medical University; senior teacher of maxillofacial surgery and surgical dentistry department S.M. Kirov Military Medical Academy Ministry of Defense of Russia. E-mail: slnzub@gmail.com ORCID: https://orcid.org/0000-0002-4359-2179

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Abstract. Based on the dynamic observation of the oral cavity condition of 49 (26 boys and 23 girls) children aged 5 to 8 years, of which 23 children suffered from diabetes mellitus, the impact of the disease under consideration on the condition and level of individual oral hygiene was assessed. During the year, the children used ASEPTA KIDS toothpaste for oral care. It was found that children with type I diabetes mellitus, more often than healthy children, suffer from periodontal inflammatory pathology, and their dental caries proceeds more intensively. Optimal indicators of their dental health are achieved provided that professional oral hygiene is carried out quarterly. Carrying out preventive work with parents and children in order to increase the level of dental literacy, as well as age-appropriate oral care products in sufficient quantities can significantly reduce inflammatory processes in the oral cavity.

Key words: *children; diabetes mellitus; dental health of children; teeth; hygiene of an oral cavity; hidden inflammation of a gingiva; toothpaste*

ПАТОЛОГИЯ ПОЛОСТИ РТА У ДЕТЕЙ ПРИ САХАРНОМ ДИАБЕТЕ

© Людмила Николаевна Солдатова[1, 2], Андрей Константинович Иорданишвили[1, 3], Анастасия Вадимовна Федорова[1, 4]

[1] Военно-медицинская академия им. С.М. Кирова. 194044, Санкт-Петербург, ул. Академика Лебедева, 6
[2] Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова. 197022, Санкт-Петербург, ул. Льва Толстого, 6–8
[3] Санкт-Петербургский медико-социальный институт. 195271, Санкт-Петербург, Кондратьевский пр., 72 А
[4] ООО «Медвед». 196634, Санкт-Петербург, п. Шушары, ул. Ростовская, 17/4 А

Контактная информация:
Людмила Николаевна Солдатова — д.м.н., доцент, профессор кафедры стоматологии детского возраста и ортодонтии ПСПбГМУ им. акад. И.П. Павлова; старший преподаватель кафедры челюстно-лицевой хирургии и хирургической стоматологии ВМедА им. С.М. Кирова. E-mail: slnzub@gmail.com ORCID: https://orcid.org/0000-0002-4359-2179

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Резюме. На основании динамического наблюдения за состоянием полости рта 49 детей (26 мальчиков, 23 девочки) в возрасте от 5 до 8 лет, из которых 23 ребенка страдали сахарным диабетом, проведена оценка влияния рассматриваемого заболевания на состояние и уровень индивидуальной гигиены полости рта. В течение года дети использовали для ухода за полостью рта зубную пасту «АСЕПТА KIDS». Установлено, что дети с сахарным диабетом 1-го типа чаще, чем здоровые дети, страдают воспалительной патологией пародонта, а кариес зубов у них протекает более интенсивно. Оптимальные показатели их стоматологического здоровья достигаются при условии проведения профессиональной гигиены полости рта ежеквартально. Проведение профилактической работы с родителями и детьми с целью повышения уровня стоматологической грамотности, а также соответствующие возрасту средства по уходу за полостью рта, позволяют значительно уменьшить воспалительные процессы в полости рта.

Ключевые слова: *дети; сахарный диабет; стоматологическое здоровье детей; патология полости рта; гигиена полости рта; скрытое воспаление десны; зубная паста*

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Diabetes mellitus (DM) is defined as a dysmetabolic systemic disease that disrupts many types of metabolism in the human body, including carbohydrate metabolism. As a result of these disorders, macro- and microangiopathies are formed, which can be considered as one of the numerous complications of this disease [1, 2]. Complex neuroendocrine mechanisms lead to morphofunctional changes in many organs and systems of the human body at all ages [1, 3]. Type 1 diabetes mellitus (insulin-independent) occurs as a result of decreased insulin secretion by beta-cells of the pancreatic islets of Langerhans and it is less common [2, 4]. Its severe forms more often affect children and young adults (juvenile diabetes) [5]. Due to the weakening or loss of specific effects of insulin, as well as various morphofunctional and metabolic disorders in the body, dental manifestations of diabetes mellitus are noted in the vast majority of patients. Some dental specialists indicate 100% lesions of oral organs and tissues in patients suffering from diabetes mellitus [1, 5, 6]. In modern literature, the relationship between periodontal pathology and diabetes mellitus is noted [7, 8]. The authors note that when the course of endocrine pathology worsens, inflammatory changes in periodontal tissues worsen [4, 7]. The duration of remission of the inflammatory process in periodontal tissues depends on the form of diabetes mellitus [2, 4]. In children with diabetes mellitus, inflammatory processes usually occur with frequent exacerbations [5, 7].

Nowdays there is not enough attention to improving the dental health of children, as well as the prevention of exacerbations of inflammatory process in periodontal tissues in them, despite the large number of complications of diabetes mellitus in the oral cavity.

The aim of our study was to investigate the pathology of the oral cavity and improve the condition of periodontal tissues in children with diabetes mellitus.

MATERIALS AND METHODS

The study included 49 children (26 boys and 23 girls) aged 5 to 8 years, living in St. Petersburg or Leningrad region. They were divided into 3 groups (Fig. 1). Dynamic observation of the children was carried out for 12 months. The 1st (control) group consisted of 26 (12 boys and 14 girls) children who did not have type 1 diabetes mellitus. Group 2 included 12 children (7 boys and 5 girls) with mild to moderate type 1 diabetes mellitus and an average disease duration of 24 months. Group 3 consisted of 11 children (6 boys and 5 girls) with mild to moderate type 1 diabetes mellitus with an average disease duration of 29 months. Therapeutic and preventive measures were carried out for children of all three groups due to the condition of the hard tissues of the teeth and periodontal. Parents were counselled on the care of children's teeth and oral cavity, including recommendations on the use of toothbrushes and toothpastes. Children in group 2 received dental treatment and preventive measures 2 times a year, and children in group 3 — once a quarter. Children of the three observation groups were provided with gel-based toothpaste "ACEPTA KIDS" after completion of oral cavity sanitation, which would be sufficient for them to use for 12 months. Calcium lactate in its composition strengthens and mineralises the tooth enamel of deciduous and permanent teeth, while extracts of chamomile and aloe provide an anti-inflammatory effect. The paste does not contain aggressive components, so it is completely safe to swallow and is suitable for regular use.

The degree of dental caries was determined using the following indicators: prevalence and intensity. The PMA index according to C. Parma (1968) and periodontal index (PI) according to Russel (1971) were used in order to assess the periodontal condition in patients of the three groups. In order to detect latent inflammation in periodontal tissues Schiller-Pisarev test and oral hygiene index according to Yu. Volodkina [3, 4] were used. In-depth study of the children's dental status was carried out 6 and 12 months after the beginning of dynamic follow-up.

The criterion for excluding children from the clinical study was general somatic diseases, namely the combination of diabetes mellitus with other endocrine diseases and the child's inability to independently and fully care for his or her teeth.

The study performed was in full compliance with the ethical standards of the Committee on

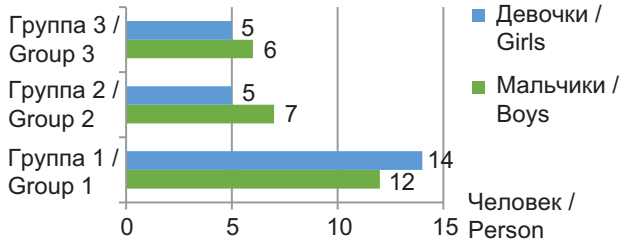


Fig. 1. Distribution of children by gender in the study groups (persons)

Рис. 1. Распределение детей по полу в исследуемых группах (чел.)

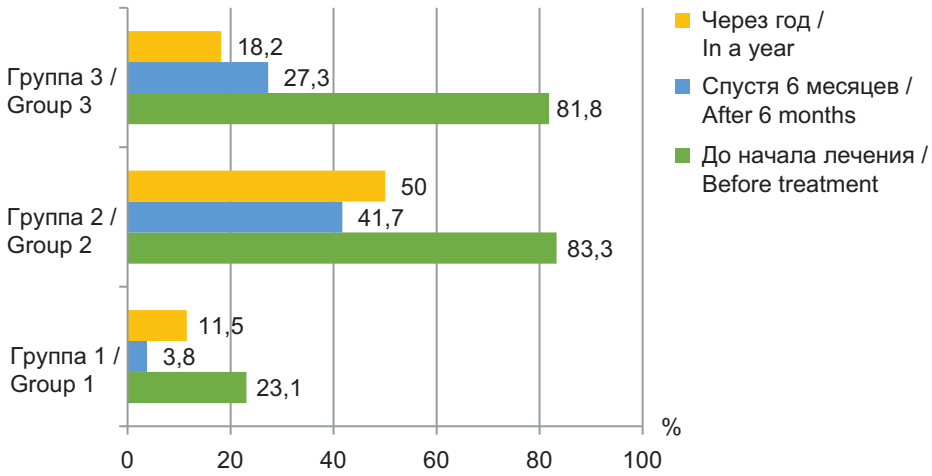


Fig. 2. Incidence of gingivitis in children in the study groups (%)

Рис. 2. Частота встречаемости гингивита у детей в исследуемых группах (%)

Human Experiments of the Helsinki Declaration on Human Experiments of 1975 and its 2000 revision.

The digital material obtained from the clinical study was processed on a PC using a specialised statistical analysis package — STATISTICA 7.0 for Windows. Differences between the compared groups were considered reliable at $p \leq 0.05$.

RESULTS

The value of dental caries intensity index in children of the control group was 4.06±0.27, which corresponds to a compensated process. In children of the 2nd and 3rd groups the intensity index was 6.86±0.23 and 6.89±0.31 ($p \leq 0.05$), which showed a subcompensated process of the carious process. In children of groups 2 and 3 suffering from diabetes mellitus, inflammatory periodontal diseases were more frequent. Catarrhal gingivitis and periodontitis were detected in 10 (83.3%) and 2 (16.7%) children of group 2, and in 9 (81.8%) and 2 (18.2%) children of group 3 respectively. Catarrhal inflammation of the gingiva was detected in 6 (23.1%) children in the control group. A positive Schiller-Pisarev test was detected in all children (100%) with diabetes mellitus and in 7 (26.9%) children from group 1. The indicators of individual oral hygiene were also worse in children with diabetes mellitus (Fig. 2), which was confirmed by the PMA index and periodontal index (Figs. 3, 4).

The analysis of the material showed that there were no sex differences in the frequency of occurrence and intensity of the caries in children of the control group and those suffering from DM ($p \geq 0.05$). As a result of the study, we found no fundamental differences between the data obtained on periodontal pathology in children with diabetes mellitus and the data of other authors.

In the clinical study we noted that when the course of DM worsens, the pathological process in the periodontium worsens, and remissions have a positive effect on it. The specific feature of the course of inflammatory periodontal pathology in children of 5–8 years old suffering from DM is the presence of frequent exacerbations of inflammatory gingival pathology, more pronounced oedema and congestive hyperaemia of the gingiva, its friability and bleeding, as well as pathological mobility of teeth (Fig. 6, a).

The study of the dental status after 6 months (Fig. 6, b) showed that dental health improved in children of all groups studied. Thus, in the control group, individual oral hygiene improved (hygiene index 1.49±0.11), the number of individuals suffering from gingivitis decreased to 1 (3.8%), which corresponded to a positive PMA and periodontal index. After 12 months, gingivitis was determined in 3 (11.5%) children, latent gingival inflammation in 4 (15.4%) individuals, and there was a slight worsening of the PMA index and PI compared to the previous examination ($p \geq 0.05$).

Group 2 children also showed an improvement in oral hygiene scores after 6 months (hygiene index 1.85±0.09). The number of children with inflammatory periodontal pathology decreased. Catarrhal gingivitis was detected in 5 (41.7%) children and a positive Schiller-Pisarev test in 4 (33.3%), which corresponded to the PMA index and periodontal index (Figs. 2, 3). One year later, gingivitis was determined in 6 (50%) children and the latent gingival inflammation — in 5 (41.7%) people. The PMA index ($p \geq 0.05$) and PI index

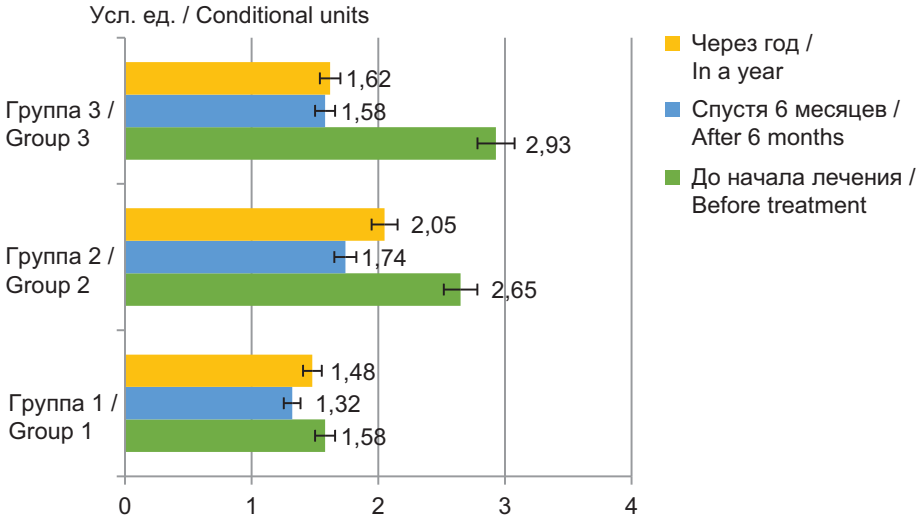


Fig 3. Hygiene index indicators Yu.A. Fedorova - V.V. Volodkina during dynamic observation of children in the studied groups (conventional units)

Рис. 3. Показатели индекса гигиены Ю.А. Федорова – В.В. Володкиной в ходе динамического наблюдения за детьми в исследуемых группах (усл. ед.)

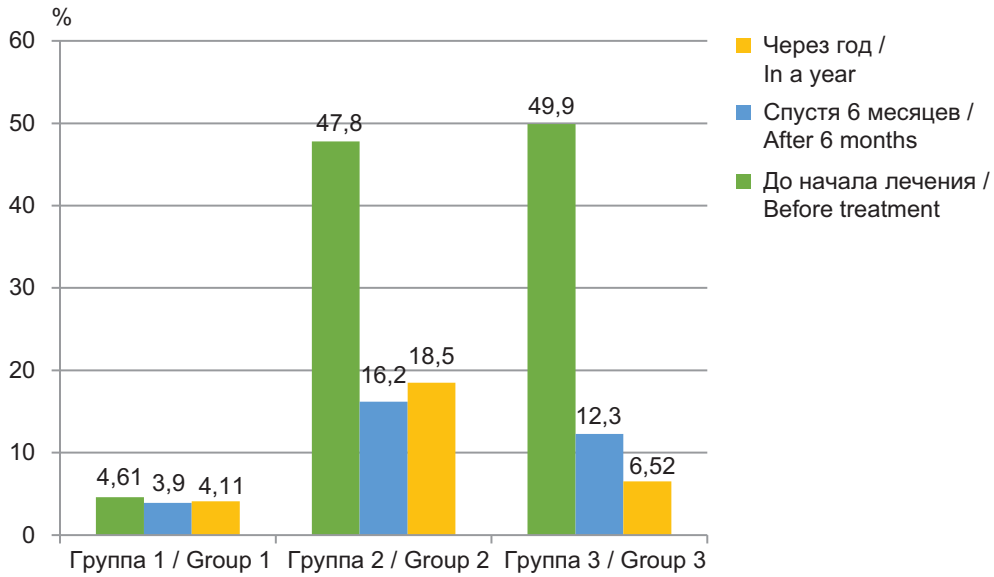


Fig 4. RMA index values during dynamic observation of children in the study groups (%)

Рис. 4. Значения индекса РМА в ходе динамического наблюдения за детьми в исследуемых группах (%)

(p ≤0.05) slightly worsened compared to the previous examination.

In group 3 children oral hygiene significantly improved after 6 months (hygiene index 1.73±0.17) and inflammatory periodontal pathology decreased. Catarrhal gingivitis was detected in 3 (27.3%) children, and a positive Schiller-Pisarev test — in 4 (36.4%) (Fig. 5). Positive dynamics of the PMA index and periodontal index were observed (Figs. 2, 3). The dental health of children in Group 3 improved markedly after one year compared to the previous examination. Thus, catarrhal gingivitis was determined only in 2 (18.2%) children, and latent gingival inflammation — in 3 (27.8%) people. Positive dynamics (Figs. 2, 3) of oral hygiene indexes (p ≥0.05), PMA (p ≤0.05) and PI (p ≤0.05) were observed.

CONCLUSION

The study of the oral cavity of children with endocrine pathology has allowed us to establish that they suffer from inflammatory periodontal diseases (gingivitis, periodontitis) more often than healthy children. According to the results of the clinical study, taking into account the therapeutic and preventive measures aimed at improving the oral cavity of children with type 1 diabetes mellitus, optimal indicators of dental health are achieved if professional oral hygiene

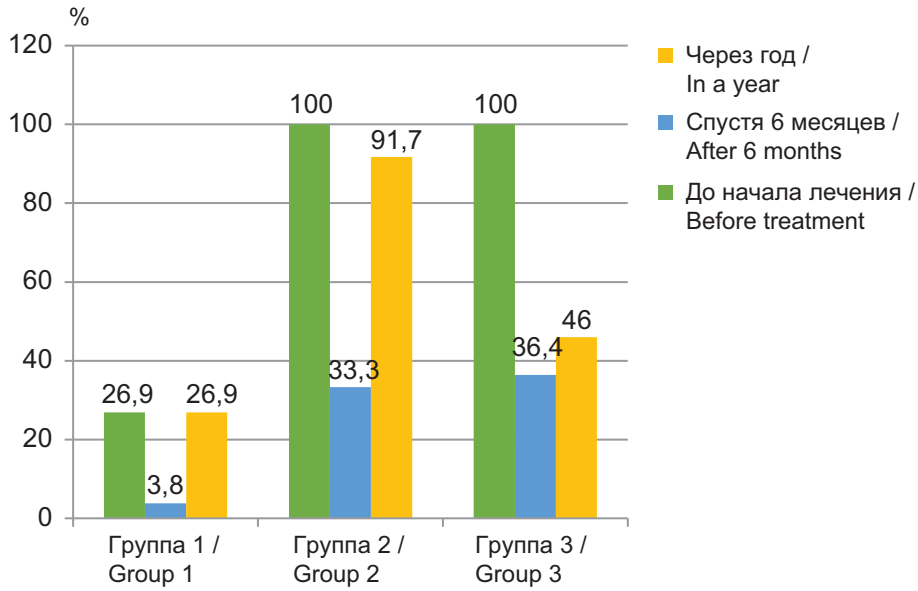
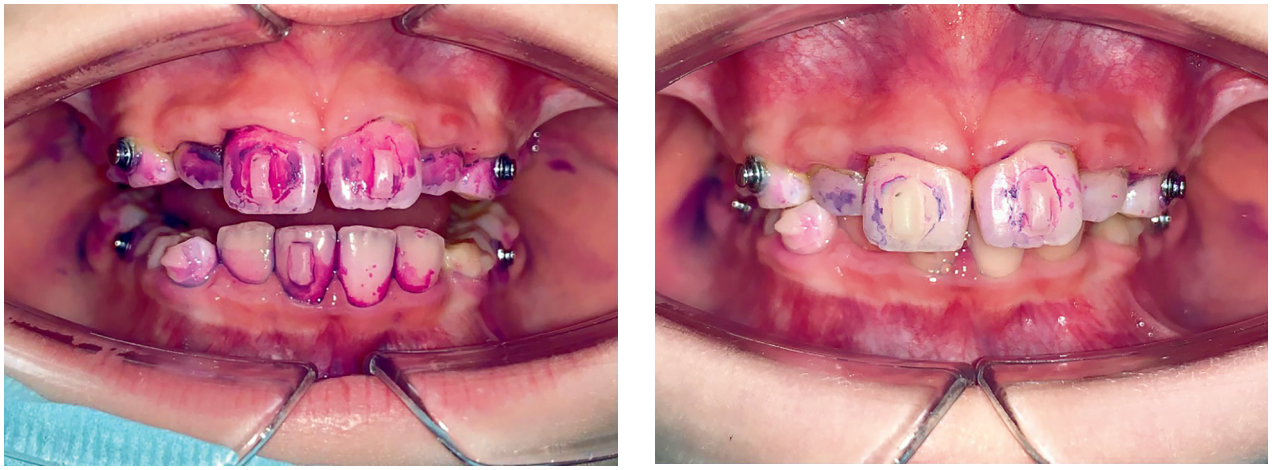


Fig. 5. Frequency of occurrence of a positive Schiller-Pisarev test during dynamic observation of children in the study groups (%)

Рис. 5. Частота встречаемости положительной пробы Шиллера–Писарева в ходе динамического наблюдения за детьми в исследуемых группах (%)



а/a *б/b*

Fig. 6. The state of oral hygiene in an 8-year-old girl suffering from type 1 diabetes mellitus: *a* — before treatment; *b* — 6 months after treatment

Рис. 6. Состояние гигиены полости рта у девочки 8 лет, страдающей сахарным диабетом 1-го типа: *а* — до лечения; *б* — через 6 месяцев после проведенного лечения

is carried out quarterly. Preventive work with parents and children to improve dental literacy and age-appropriate oral care products can significantly reduce inflammatory processes in the oral cavity.

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 the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи,

прочли и одобрили финальную версию перед публикацией.

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

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

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

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THE STUDY OF THE PSYCHOMETRIC PROPERTIES OF THE RUSSIAN-LANGUAGE ADAPTED VERSION «BABY EATING BEHAVIOUR QUESTINANAIRE»

© Severin V. Grechanyi

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Severin V. Grechanyi — Doctor of Medical Sciences, Associate Professor, Head of the Department of Psychiatry and Narcology.
E-mail: svgrechany@mail.ru ORCID: 0000-0001-5967-4315

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Abstract. Due to the active study of anorexic and bulimic disorders in infancy and early childhood, there is currently a shortage of objective examination methods, including rating questionnaires. *The aim of the study* was to study the psychometric properties of the adapted version of the "Infant Eating Behavior Questionnaire" to assess the suitability of this test in the Russian-speaking population. 227 mothers were tested once, whose infants (100 boys, 127 girls, p=0.073, age 1–7 months) underwent a routine preventive outpatient examination in four district polyclinics of St. Petersburg in the period from September 2019 to May 2021. *Method*: exploratory factor analysis, the "maximum likelihood" method, varimax-rotation. *Results*: the Kaiser-Mayer-Olkin sample adequacy measure (0.655) and the Bartlett sphericity criterion (χ^2=717.768, df=153, p=0.0001) showed conditional suitability of the data array for statistical analysis. The total cumulative variance was 53.469%. Based on the constructed graph of the eigenvalues of the principal components, the applied Kaiser and R. Kettel criteria, a 5-factor model was selected with the criterion "quality of fit", indicating the completeness of factorization (χ^2=90.256, df=73, p=0.083). Thus, the 5-factor scale structure of the questionnaire, typical for the original version, was confirmed. However, the components of the scales did not correspond to the original version. The scale "Food responsiveness" in the Russian version included only 4 original items (2, 8, 14, 16). The rest belong to the scale of "Enjoyment of food" (point 1 with a reverse calculation), the scale of "Satiety responsiveness" (points 7 and 13) and the scale of "Slowness in eating" (point 15). The "Enjoyment of food" scale included only one item present in the original version (17). The other two (12 and 18) in the original version belong to the "Food responsiveness" scale. The "Satiety responsiveness" scale contains only two points — 5 and 10. And only the latter reflects the studied property. The "Slowness in eating" scale is represented by only two items (9 and 11), they both belong to the same scale in the original version. Of all the scales, only the "Slowness in eating" scale demonstrates acceptable statistical consistency (Cronbach's α >0.7). The Cronbach's α value of the "Food responsiveness" scale (>0.6) is in the range of questionable suitability. Other scales have a Cronbach's α value of less than 0.6. The article discusses the reasons for the discrepancy between the components of the scales of the original version and the version obtained in this work, as well as the low degree of consistency of the questionnaire items within the selected scales.

Key words: *infant eating behavior; infantile anorexia; infantile bulimia; infant eating behavior questionnaire; early childhood-maternal interaction*

ИЗУЧЕНИЕ ПСИХОМЕТРИЧЕСКИХ СВОЙСТВ РУССКОЯЗЫЧНОГО АДАПТИРОВАННОГО ВАРИАНТА «ОПРОСНИКА ПИЩЕВОГО ПОВЕДЕНИЯ МЛАДЕНЦЕВ»

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Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Северин Вячеславович Гречаный — д.м.н., доцент, заведующий кафедрой психиатрии и наркологии.
E-mail: svgrechany@mail.ru ORCID: 0000-0001-5967-4315

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Резюме. В связи с активным изучением аноректических и булимических расстройств в младенческом и раннем детском возрасте в настоящее время отмечается дефицит объективных методик обследования, в том числе рейтинговых опросников. *Целью исследования* было изучение психометрических свойств адаптированной версии «Опросника пищевого поведения младенцев» для оценки пригодности данного теста в русскоязычной популяции. *Материалы и методы:* Однократно было протестировано 227 матерей, чьи младенцы (100 мальчиков, 127 девочек, p=0,073, возраст 1–7 месяцев) проходили плановый профилактический амбулаторный осмотр в четырех районных поликлиниках города Санкт-Петербурга в период с сентября 2019 г. по май 2021 г. Применялись эксплораторный факторный анализ, метод «максимум правдоподобия», варимакс-вращение. *Результаты*: мера адекватности выборки Кайзера–Майера–Олкина (0,655) и критерий сферичности Бартлетта (χ^2=717,768, df=153, p=0,0001) показали условную пригодность массива данных для статистического анализа. Суммарная совокупная дисперсия составила 53,469%. На основании построенного графика собственных значений главных компонент, примененных критериев Кайзера и Р. Кеттела была выбрана 5-факторная модель с критерием «качество подгонки», свидетельствующим о полноте факторизации (χ^2=90,256, df=73, p=0,083). Таким образом, была подтверждена 5-факторная шкальная структура опросника, типичная для оригинальной версии. Однако составляющие шкал не соответствовали оригинальной версии. Шкала «Желание поесть» в русскоязычном варианте включила только 4 оригинальных пункта (2, 8, 14, 16). Остальные относятся к шкале «Удовольствие от приема пищи» (пункт 1 с обратным подсчетом), шкале «Чувствительность к перееданию» (пункты 7 и 13) и шкале «Медленный темп приема пищи» (пункт 15). Шкала «Удовольствие от приема пищи» включила в себя только один присутствующий в оригинальной версии пункт (17). Два других (12 и 18) в оригинальной версии принадлежат к шкале «Желание поесть». Шкала «Чувствительность к перееданию» содержит всего два пункта — 5 и 10. И только последний отражает изучаемое свойство. Шкала «Медленный процесс приема пищи» представлена всего двумя пунктами (9 и 11), они оба относятся к такой же шкале в оригинальной версии. Из всех шкал только шкала «Медленный процесс приема пищи» демонстрирует приемлемую статистическую согласованность (α Кронбаха >0,7). В диапазоне сомнительной пригодности находится значение α Кронбаха шкалы «Желание поесть» (>0,6). Другие шкалы имеют значение α Кронбаха меньше 0,6. В статье обсуждаются причины несоответствия составляющих шкал оригинальной версии и версии, полученной в настоящей работе, а также низкую степень согласованности пунктов опросника в рамках выделенных шкал.

Ключевые слова*: пищевое поведение младенцев; инфантильная анорексия; инфантильная булимия; опросник пищевого поведения младенцев; раннее детско-материнское взаимодействие*

The relationship between eating behaviour in infancy and eating habits in later life, including various anorectic and bulimic syndromes, has been actively studied. Moreover, while the clinical manifestations of anorexia in infants and young children are described quite comprehensively in foreign and domestic literature and their study is supplemented by the description of new forms of disorders (for example, "Avoidant restrictive food intake disorder"), the psychological mechanisms of bulimia and overeating in children are given much less space. Although the new classification of mental disorders of the first 5 years of life, Disorders in Infancy and Early Childhood (DC:0–5), includes a diagnosis of "Infantile Overeating" in the section on Eating Disorders [1]. The lack of information on the mechanisms of overeating in this age group is quite significant. This is due to methodological difficulties in objectively assessing appetite. While for older children it has been possible to trace the role of externalised mechanisms in the onset of obesity [2, 3], it is much more difficult to study the role of external food signals, such as the sight and smell of tasty food, on the appetite of infants due to the lack of stable perceptions ("sensory standards") of what is tasty food at this age.

However, even in these conditions we managed to establish some regularities. It has been shown that differences in the eating behaviour of obesity-prone infants compared to normal-weight infants can be detected already in the first few weeks of life. For example, a high risk of obesity calculated on the basis of parental weight was associated with a more "greedy" breastfeeding style [4]. Initiation of breastfeeding by a child in the first 6 months of life predicts overweight during the second six months of life [5].

A large number of known works are devoted to the study of the relationship between eating behaviour and weight in children over 3 years old. For example, obese or overweight children have been found to have a higher rate of eating behaviour than leaner peers [6]. Also they respond more strongly to

food reinforcement stimuli [7, 8]. Obese children also show less sensitivity to internal satiety cues, causing food intake not to slow down [9].

The original version of the Baby eating behaviour Questinanaire (BEBQ) [6] was based on the Children's eating behaviour Questinanaire (CEBQ), which measures 8 eating behaviour characteristics associated with being overweight or underweight in children 3–13 years old [10]. The BEBQ consists of 18 items, 17 of which relate to 4 scales — 'Desire to eat', 'Enjoyment of eating', 'Sensitivity to overeating', 'Slow eating', and one item is a separate dimension called 'General appetite'. The result for each item is rated on a 5-point scale: 1 — never, 2 — rarely, 3 — sometimes, 4 — often, 5 — always. The scale "Desire to eat" characterises in general the child's reaction to food, i.e. the degree of sensitivity of the child to external stimuli associated with the feeding situation, the degree of the child's interest in eating, as well as such traits as "greediness", "insatiability" and violation of control over the amount eaten. The scale "Pleasure from eating" reflects the expression of positive/negative emotions arising in the process of breastfeeding. The Sensitivity to Overeating scale measures the baby's ability to regulate his/her food cravings during feeding based on the perception of satiety threshold. The Slow Eating Process scale characterises the slow rate at which the infant absorbs food.

AIM OF THE STUDY

To examine the psychometric properties of the adapted version of the Baby Eating Behaviour Questionnaire, such as factor structure and internal consistency, to assess the suitability of this test for the Russian-speaking population.

MATERIALS AND METHODS

An adapted version of the Baby Eating Behaviour Questionnaire was used, obtained by translating from English the original version of the Baby eating behaviour questinanaire. The translation work was carried out by two professionals with specialised knowledge in philology, which showed an almost complete overlap between all items, due to the originally specific and rather concise wording of the original version.

Patient recruitment and selection criteria

The study was conducted in 4 district polyclinics in St. Petersburg from September 2019 to May 2021 with short breaks. Mothers who met the selection criteria were asked to fill in the questionnaire after signing the voluntary informed consent of the study participant during routine medical check-ups of children of the first year of life.

Inclusion criteria: 1) mothers of children 1–7 months old who underwent the routine preventive ambulatory examination; 2) a voluntary consent of the study participants to fill in the questionnaire, confirmed by written completion of a specially designed form; 3) the understanding by the participant of the study of its purpose, as well as the content and meaning of the questions contained in the text of the questionnaire, and a positive attitude to the study. **Non-Inclusion criteria:** 1) a lack of understanding of the meaning of the questions in the questionnaire; 2) an evidence of an acute psychiatric history in the child's mother, observation by a psychiatric institution or planned psychiatric treatment. **Exclusion criterion:** a refusal of further participation in the study, confirmed in writing form or verbally.

The study was an one-stage. The results were analysed and interpreted by a mental health professional (psychiatrist) experienced in working with children, including those in the first year of life, and their mothers.

Initially, 232 mothers were invited to participate in the study. During the study, 5 people refused to complete the questionnaire due to "lack of free time" and "impossibility to come to the polyclinic again" (the questionnaires were submitted in paper form only).

Statistical analysis

Absolute value (n) and % in group were used to describe qualitative (categorical) variables. Pearson's χ^2 criterion was used to compare qualitative variables on the basis of conjugation tables. Quantitative parametric variables were described on the basis of mean (M) and standard deviation (sd), non-parametric variables — median (Me) and 25% and 75% quartiles. The values of asymmetry (As) and excess (Ex) and their standard errors (p) were used to test the normality of the distribution. A sample was considered to conform to a normal distribution if the absolute values of As and Ex did not exceed their standard errors [11]. Parametric comparison of groups was carried out on the basis of Student's t-criterion, nonparametric — on the basis of Mann-Whitney's U criterion. Exploratory factor analysis was used to calculate the suitability of the array for its use (Kaiser–Mayer–Olkin and Bartlett) to reduce the dimension. Kaiser and R. Kettel criteria were chosen to select the required number of factors [11].

Mothers of 227 children — 100 boys, 127 girls — were tested (sex difference was statistically unreliable: χ^2=3.211, df=1, p=0.073). The children ranged in age from 38 to 231 days, with

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a mean of 102.97 (43.712) days. There were no sex differences in characteristics such as age of children, gestational age at birth, age of mother and father, number of pregnancies and children in the family (Table 1). However, prematurity was significantly more common among boys (p=0.023).

Factor analysis and its results

Preliminary results of the calculation showed the conditional suitability of the data set for exploratory factor analysis. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.655. Bartlett's criterion of sphericity was χ^2=717.768, df=153, p=0.0001.

The explained cumulative variance based on principal components is presented in Table 2. The table shows that the number of principal components with factor loading above 1.0 is 5 with an aggregate variance of 53.395%.

The graph of eigenvalues of principal components is presented in Figure 1. The graph shows that there are 5 factors above the eigenvalue equal

Table 1. General characteristics of the study participants

Таблица 1. Общая характеристика участников исследования

Characteristics Характеристики	Total (n=227, 100,0%) Всего (n=227, 100,0%)	Boys (n=100, 44,1%) Мальчики (n=100, 44,1%)	Girls (n=127, 55,9%) Девочки (n=127, 55,9%)	Reliability differences Достоверность различий
Age of children, days / Возраст детей, дни M (sd) min-max Me [Q25; Q 75] As (p) Ex (p)	 102,97 (43,712) 38–231 92,00 [70,00; 122,00] 0,892 (0,162) –0,081 (0,322)	 104,06 (44,188) 42–231 98,50 [66,25; 126,00] 0,840 (0,241) –0,059 (0,478)	 102,12 (43,490) 38–206 91,00 [71,00; 122,00] 0,945 (0,215) –0,047 (0,427)	p=0,661 by the Mann-Whitney's U criterion / p=0,661 по критерию U Манна–Уитни
Gestational age / Гестационный возраст M (sd) min-max Me [Q25; Q 75] As (p) Ex (p)	 38,86 (2,075) 24–42 39,00 [38,00; 40,00] –2,836 (0,162) 13,797 (0,322)	 38,50 (2,560) 24–42 39,00 [38,00; 40,00] –2,690 (0,241) 10,759 (0,478)	 39,15 (1,543) 31–42 39,00 [39,00; 40,00] –1,847 (0,215) 7,362 (0,427)	p=0,064 by the Mann-Whitney's U criterion / p=0,064 по критерию U Манна–Уитни
Mother's age, years / Возраст матери, годы M(sd) min-max Me [Q25; Q 75] As (p) Ex (p)	 29,67 (5,122) 17–45 30,00 [26,00; 33,00] 0,077 (0,162) 0,199 (0,322)	 30,30 (5,528) 19–45 31,00 [27,00; 33,75] 0,375 (0,241) 0,119 (0,478)	 29,17 (4,740) 17–41 30,00 [26,00; 32,00] –0,409 (0,215) –0,218 (0,427)	p=0,269 by the Mann-Whitney's U criterion / p=0,269 по критерию U Манна–Уитни
Fother's age, years / Возраст отца, годы M(sd) min-max Me [Q25; Q 75] As (p) Ex (p)	 31,44 (5,112) 18–52 31,00 [28,00; 34,00] 0,785 (0,162) 2,065 (0,322)	 32,17 (5,803) 20–52 31,00 [28,00; 35,00] 1,083 (0,241) 1,705 (0,478)	 30,86 (4,434) 18–45 31,00 [28,00; 33,25] –0,409 (0,215) –0,218 (0,427)	p=0,303 by the Mann-Whitney's U criterion / p=0,303 по критерию U Манна–Уитни
What's your pregnancy count? / Какая по счету беременность?				
The 1 st / 1-я	68 (30,0%)	32	36	χ^2=3,317, df=6, p=0,768
The 2 nd / 2-я	64 (28,2%)	26	38	
The 3 rd / 3-я	38 (16,7%)	18	20	
The 4 th / 4-я	16 (7,0%)	9	7	
The 5 th / 5-я	3 (1,3%)	1	2	
The 6 th / 6-я	1 (0,4%)	–	1	
The 7 th / 7-я	1 (0,4%)	–	1	
Missing values / Пропущенные значения	36 (15,9%)	14 (6,2%)	22 (9,7%)	
Valid / Валидные	191 (84,1%)	86 (37,9%)	105 (46,3%)	
Total / Всего	227 (100,0%)	100 (44,1%)	127 (55,9%)	

Окончание табл. 1

Characteristics Характеристики	Total (n=227, 100,0%) Всего (n=227, 100,0%)	Boys (n=100, 44,1%) Мальчики (n=100, 44,1%)	Girls (n=127, 55,9%) Девочки (n=127, 55,9%)	Reliability differences Достоверность различий
What's the baby's count? /Какой по счету ребенок?				
The 1 st / 1-й	118 (52,0%)	56	62	χ^2=3,897, df=3, p=0,273
The 2 nd / 2-й	86 (37,9)	37	49	
The 3 rd / 3-й	21 (9,3)	6	15	
The 4 th / 4-й	1 (0,4%)	1	0 (0,0%)	
Missing values / Пропущенные значения	1 (0,4%)	(0,0%)	1	
Total / Всего	227 (100,0%)	100 (44,1%)	127 (55,9%)	
Prematurity / Недоношенность				
No / Нет	216 (95,2%)	91 (40,1%)	125 (55,1%)	χ^2=5,176, df=1, p=0,023*
Yes: / Да Of them / Из них:	11 (4,8%)	9 (4,0%)	2 (0,9%)	
24 weeks / 24 нед 31 weeks / 31 нед 32 weeks / 32 нед 34 weeks / 34 нед 35 weeks / 35 нед	1 (0,4%) 2 (0,8%) 1 (0,4%) 5 (2,2%) 2 (0,8%)	1 (0,4%) 1 (0,4%) 1 (0,4%) 5 (2,2%) 1 (0,4%)	0 (0,0%) 1 (0,4%) 0 (0,0%) 0 (0,0%) 1 (0,4%)	χ^2=4,278, df=4, p=0,370
Total / Всего	227 (100,0%)	100 (44,1%)	127 (55,9%)	
Mean age, days: Premature infants / Средний возраст, дни: Недоношенные	32,55 (3,174) 24–35 34,00 [31,00; 34,00]	32,44 (3,392) 24–35 34,00 [31,50; 34,00]	33,00 (2,828) 31–35 34,00 [31,00; 34,00]	p=0,909 by the Mann-Whitney's U criterion / p=0,909 по критерию U Манна–Уитни

Table 2. Explained cumulative variance

Таблица 2. Объясненная совокупная дисперсия

Component / Компонент	The initial eigenvalues / Начальные собственные значения			The extracted sum of squares of loads / Извлечение суммы квадратов нагрузок		
	total / всего	% variance / % дисперсии	cumulative % / суммарный %	total / всего	% variance / % дисперсии	cumulative % / суммарный %
1	2,931	16,284	16,284	2,931	16,284	16,284
2	2,061	11,452	27,736	2,061	11,452	27,736
3	1,909	10,603	38,339	1,909	10,603	38,339
4	1,433	7,962	46,301	1,433	7,962	46,301
5	1,290	7,168	53,469	1,290	7,168	53,469
6	0,977	5,429	58,898			
7	0,913	5,075	63,973			
8	0,866	4,812	68,785			
9	0,800	4,442	73,227			
10	0,770	4,275	77,502			
11	0,698	3,880	81,382			
12	0,640	3,557	84,939			
13	0,550	3,056	87,995			
14	0,503	2,793	90,787			
15	0,464	2,578	93,365			
16	0,447	2,485	95,850			
17	0,423	2,349	98,200			
18	0,324	1,800	100,000			

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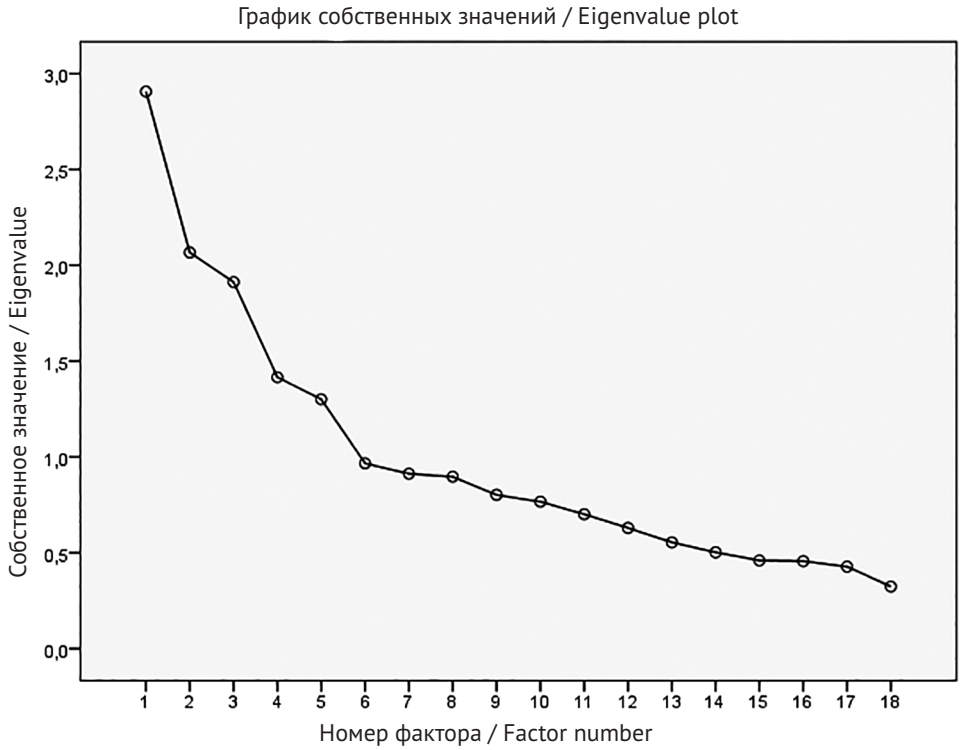

Fig. 1. Graph of eigenvalues of principal components

Рис. 1. График собственных значений главных компонент

Table 3. Indicators of "quality of fit" under 5- and 6-structural factor model

Таблица 3. Показатели «качества подгонки» при 5- и 6-структрной факторной модели

Structure / Структура	A consensus criterion χ^2 / Критерий согласия χ^2	The degree of freedom / Степени свободы (degree freedom)	A significance level / Уровень значимости
5-structural factor model / 5-факторная структура	90,256	73	0,083
6-structural factor model / 6-факторная структура	67,109	60	0,247

to 1.0. The curve of the graph (an exit to a gentle straight line after a sharp decline) is observed at the level of the 6th factor. Therefore, the assumptions of 5 or 6 factors were tested.

The "maximum likelihood" method was chosen as the factorization method, which makes it possible to assess the completeness of factorization based on the distribution of residual correlation coefficients. The indicators of "quality of fit" — χ^2 agreement criteria of the extracted factors at 5- and 6-structural model are presented in Table 3. Table 3 shows that in both cases the level of significance based on the χ^2 concordance criterion is above 0.05, indicating a sufficient number of extracted factors in both cases, i.e. in the case of both 5- and 6-factor structure. However, only in the case of the 5 structural model the eigenvalues of the factors are higher than 1.0 (the Kaiser's criterion), the final choice is made in favour of the 5 factor model.

The rotated factor matrix obtained using the varimax-rotation method is presented in Table 4. Based on the prevalence of factor loadings, the items of the questionnaire were selected as part of the five factors corresponding to the five scales of the questionnaire. Table 4 shows that item 6 ("My child is upset at feeding time"), which had loadings on any of the factors less than 0.3, was not included in any of the scales and was excluded from the questionnaire. Two items (1 and 7) had negative loadings on the first factor, which gives reason to apply the principle of backward counting when processing the collected data (5 — never, 4 — rarely, 3 — sometimes, 2 — often, 1 — always).

The reliability analysis of the scales of the "Baby Eating Behaviour Questionnaire" based on the values of α Cronbach's is presented in Table 5. Factor loadings are indicated in parentheses with item numbers. As can be seen from Table 5, only the 4th scale ("Slow

Table 4. Rotated factor matrix of the 5 factor structure of the Baby Eating Behaviour Questinanaire
Таблица 4. Повернутая факторная матрица 5-факторной структуры «Опросника пищевого поведения младенцев»

	Factor analysis / Факторный анализ				
	1	2	3	4	5
Point 1 / Пункт 1	–0,353	–0,053	0,130	0,206	0,217
Point 2 / Пункт 2	0,412	0,083	0,045	0,104	–0,006
Point 3 / Пункт 3	–0,188	–0,019	0,007	0,710	0,142
Point 4 / Пункт 4	0,276	–0,090	–0,169	0,473	–0,012
Point 5 / Пункт 5	0,018	0,146	0,462	–0,030	–0,107
Point 6 / Пункт 6	–0,255	0,270	–0,025	0,023	–0,033
Point 7 / Пункт 7	–0,514	0,103	0,277	–0,019	0,084
Point 8 / Пункт 8	0,506	–0,154	–0,089	0,446	0,051
Point 9 / Пункт 9	0,185	0,631	–0,014	–0,031	0,215
Point 10 / Пункт 10	–0,042	–0,149	0,901	–0,092	0,051
Point 11 / Пункт 11	0,081	0,882	0,120	–0,140	–0,011
Point 12 / Пункт 12	0,179	0,031	–0,113	0,129	0,419
Point 13 / Пункт 13	0,397	0,156	0,062	–0,068	–0,021
Point 14 / Пункт 14	0,494	0,021	–0,051	0,039	0,089
Point 15 / Пункт 15	0,557	0,050	0,102	–0,003	–0,111
Point 16 / Пункт 16	0,507	–0,139	–0,161	–0,043	0,297
Point 17 / Пункт 17	–0,291	0,164	0,033	0,240	0,449
Point 18 / Пункт 18	–0,057	0,038	0,008	–0,052	0,652

Table 5. Constituent scale items and reliability analysis of the Baby Eating Behaviour Questionnaire scales
Таблица 5. Составляющие шкалы пункты и анализ надежности шкал «Опросника пищевого поведения младенцев»

Scales /Шкалы	Points / Пункты	α Cronbach's / α Кронбаха
1) Desire to eat (8 items) / 1) Желание поесть (8 пунктов)	1 (back counting / обратный подсчет) (–0,353), 2 (0,412), 7 (back counting / обратный подсчет) (–0,514), 8 (0,506), 13 (0,397), 14 (0,494), 15 (0,557), 16 (0,507)	0,684
2) The pleasure of eating (3 points) / 2) Удовольствие от приема пищи (3 пункта)	12 (0,419), 17 (0,449), 18 (0,652)	0,496
3) Sensitivity to overeating (2 points) / 3) Чувствительность к перееданию (2 пункта)	5 (0,462), 10 (0,901)	0,563
4) Slow eating process (2 points) / 4) Медленный процесс приема пищи (2 пункта)	9 (0,681), 11 (0,882)	0,726
5) General appetite (2 points) / 5) Общий аппетит (2 пункта)	3 (0,710), 4 (473)	0,434

eating process") demonstrates acceptable statistical consistency of its constituent items (α Cronbach's >0.7). In the range of doubtful suitability is the value of α Cronbach's scale "Desire to eat" (>0.6).

The comparative characteristics of the item scale components of the Babu Eating Behaviour Questionnaire in the original version and the results of the present study are presented in Table 6.

The "Desire to Eat" scale measures a number of mental and physiological processes relevant to the dynamics of the formation of a child's food sense and the degree of its maturity. The complexity and

multicomponent nature of the constituent processes is evidenced by the name of the scale, the literal translation of which into Russian ("Food responsiveness") is not only stylistically unsuccessful, but also does not fully reflect the essence of the processes under study. Out of all possible translation variants, we chose the wording "Desire to eat" because it implies: 1) the desire for food (motivational and instinctive component of eating behaviour); 2) a recognition of the situation of eating (perceptual component of eating behaviour); 3) an assessment of the fact of food availability and the upcoming feeding situation, anticipation of it (attentive and anticipatory components of eating behaviour); 4) a positive attitude to the source of food — the mother (dyadic component of eating behaviour); 5) an interest in the "technical" side of the process (cognitive component of eating behaviour). All this determines the presence of a peculiar "reaction" to food, food "responsiveness", i.e. attunement to food, special sensitivity to it — what the authors of the methodology united in the concept of "food responsiveness". It is ensured by a proper level of physiological reactivity of the digestive system, the presence of a tentative reaction to food and a positive evaluation of the feeding process.

The "Desire to eat" scale, which contains 6 items in the original version, only 4 items were included in the Russian version according to the results of our calculations. The remaining 4 items in the original version are included in other scales. Thus, an item 1, "My child seems to look satisfied during feeding" belongs to the scale "Pleasure from eating". It is important to note that in our version it is presented in a reversed form (reverse counting), i.e. the process of feeding the baby, according to the interviewed mothers, is rather associated with the experience of infant's dissatisfaction (unambiguously not associated with the experience of an emotionally positive state). An item 7 ("My baby gets full quickly"), also presented in reversed form, according to the primary source, refers to the "Sensitivity to overeating" scale. Thus, interest in infant feeding in the Russian-speaking population should be considered as a phenomenon associated with the slow eating process. The manifestation of interest in eating is also a failure to form the mechanism of the child's "control" of his/her own feeding process (an item 13 "My child finds it difficult to control his/her own feeding process"), in the original also referring to such a characteristic as "Sensitivity to overeating". Finally, also associated with food interest is the slow pace of eating (an item 15 "My baby is sucking milk more and more slowly while eating"), a feature of infant eating behaviour that is not directly related, according to the original source, to the manifestation of positive attitudes towards food.

Thus, in the proposed version of the Russian-language version of the Baby Eating Behaviour Questionnaire, one of the main scales, the "Desire to Eat" scale, is at most non-specific, as it combines both properties directly related to food interest and those measuring other characteristics of this behaviour — emotional experiences related to feeding, satiety control, and eating rate.

The Eating Enjoyment scale included only one question measuring this trait in the original version — an item 17 "My child likes feeding time". The other two items that make up the scale — an item 12 ("Even if my child has eaten well, he or she will not refuse an offer to eat") and an item 18 ("My child can easily eat again within 30 minutes after the last feeding") are the components of good appetite in the original version (the "Desire to eat" scale). That is, in the Russian-language version, the infant's satisfactory appetite and the pleasure experienced by the infant from the eating process are inseparable, which indicates a weak differentiation of individual properties of eating behaviour that have different natures and psychological purposes.

The scale "Sensitivity to overeating" included only 2 questions, one of which is directly related to the property under study — an item 10 ("My child is satiated with milk earlier than I think he should be"). The other characterises rather the rate of eating, which has some relation to the experienced feeling of satiety, but does not equate to it.

The General Appetite scale, in contrast to the original version, contains two questions, one of which is the same as in the original source — an item 4 ("My child has a strong appetite"), and the other relates to the Enjoyment of Eating scale — an item 3 ("My child likes milk").

DISCUSSION OF THE RESULTS

The calculations carried out in the present study confirmed the 5-factor structure of the Russian-language Baby Eating Behaviour Questionnaire characteristic of the original version. However, the components of the scales were far from those proposed by the authors, and the consistency index of the items composing the scales showed acceptable values in only one case (the Slow Eating Process scale). In one case, a questionable result was obtained (the "Desire to Eat" scale, α Cronbach's >0.6). And the values of the remaining three scales demonstrate unacceptable values for the test (the scales "Pleasure from eating", "Sensitivity to overeating" and "General appetite").

Table 6. Comparison of the content of the scales of the author's version of the Baby Eating Behaviour Questionnaire with the results of the present study

Таблица 6. Сравнение содержания шкал авторской версии «Опросника пищевого поведения младенцев» с результатами настоящей работы

Scales / Шкалы	Authors' of the BEVQ questionnaire version / Версия авторов опросника BEBQ	Authors' of the article version / Версия авторов статьи
1) Желание поесть (Food responsiveness, FR)	2 ("My baby wants more milk than I have") / 2 («Мой ребенок хочет больше молока, чем у меня есть»). 8 ("If possible, my baby tries to drink as much milk as possible") / 8 («По возможности мой ребенок пытается выпить как можно больше молока»). 12 ("Even if my baby has eaten well, he will not refuse an offer to eat") / 12 («Даже если мой ребенок хорошо поел, он не откажется от предложения поесть»). 14 ("My baby always demands to eat") / 14 («Мой ребенок всегда требует поесть»). 16 ("If given the chance, my baby would eat all the time") / 16 («Если бы моему ребенку был дан шанс, то он постоянно бы ел»). 18 ("My baby can easily eat again within 30 minutes of the last feeding") / 18 («Мой ребенок легко может опять поесть в течение 30 минут после последнего кормления»)	1 (reverse counting) ("My baby seems to look satisfied while feeding") - in the original scale "Pleasure with eating" / 1 (обратный подсчет) («Кажется, что мой ребенок выглядит довольным во время кормления») — в оригинале шкала «Удовольствие от приема пищи». 2 ("My baby wants more milk than I have") / 2 («Мой ребенок хочет больше молока, чем у меня есть»). 7 (reverse counting) ("My baby gets full quickly") — in the original "Sensitivity to overeating" scale / 7 (обратный подсчет) («Мой ребенок быстро наедается») — в оригинале шкала «Чувствительность к перееданию». 8 ("Whenever possible, my baby tries to drink as much milk as possible") / 8 («По возможности мой ребенок пытается выпить как можно больше молока»). 13 ("My baby finds it difficult to control his/her own feeding") — in the original "Sensitivity to overeating" scale / 13 («Моему ребенку сложно самому контролировать процесс своего кормления») — в оригинале шкала «Чувствительность к перееданию». 14 ("My baby always demands to eat") / 14 («Мой ребенок всегда требует поесть»). 15 ("My baby sucks milk more and more slowly during breastfeeding") - in the original "Slow eating process" scale / 15 («В процессе еды мой ребенок все медленнее высасывает молоко») — в оригинале шкала «Медленный процесс приема пищи». 16 ("If given the chance, my baby would eat all the time") / 16 («Если бы моему ребенку был дан шанс, то он постоянно бы ел»)
2) Удовольствие от приема пищи (Enjoyment of food, EF)	1 ("My baby seems to look happy while feeding") / 1 («Кажется, что мой ребенок выглядит довольным во время кормления»). 3 ("My baby likes milk") / 3 («Мой ребенок любит молоко»). 6 ("My baby is upset at feeding time") / 6 («Мой ребенок расстроен во время кормления»). 17 ("My baby likes feeding time") / 17 («Мой ребенок любит время кормления»)	12 ("Even if my baby has eaten well, he will not refuse an offer to eat") / 12 («Даже если мой ребенок хорошо поел, он не откажется от предложения поесть»). 17 ("My baby likes feeding time") / 17 («Мой ребенок любит время кормления»). 18 ("My baby can easily eat again within 30 minutes after the last feeding") / 18 («Мой ребенок легко может опять поесть в течение 30 минут после последнего кормления»)
3) Чувствительность к перееданию (Satiety responsiveness, SR)	7 ("My baby feeds quickly") / 7 («Мой ребенок быстро наедается») 10 ("My baby gets full earlier than I think he should") / 10 («Мой ребенок насыщается молоком раньше, чем мне кажется он должен это сделать») 13 ("It is difficult for my baby to control his/her own feeding") / 13 («Моему ребенку сложно самому контролировать процесс своего кормления»)	5 ("My baby finishes eating quickly") / 5 («Мой ребенок быстро заканчивает есть») 10 ("My baby gets full of milk earlier than I think he should") / 10 («Мой ребенок насыщается молоком раньше, чем мне кажется он должен это сделать»)

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Ending of the table 6 / Окончание табл. 6

Scales / Шкалы	Authors' of the BEVQ questionnaire version / Версия авторов опросника BEBQ	Authors' of the article version / Версия авторов статьи
4) Медленный процесс приема пищи (Slowness in eating, SE)	5 ("My baby finishes eating quickly") / 5 («Мой ребенок быстро заканчивает есть»). 9 ("The process of feeding my child takes more than 30 minutes") / 9 («Процесс кормления моего ребенка занимает более 30 мин»). 11 ("My baby eats slowly) / 11 («Мой ребенок ест медленно). 15 ("My baby is sucking milk more and more slowly while breastfeeding") / 15 («В процессе еды мой ребенок все медленнее высасывает молоко»)	9 ("The process of feeding my baby takes more than 30 minutes") / 9 («Процесс кормления моего ребенка занимает более 30 мин»). 11 ("My baby eats slowly) / 11 («Мой ребенок ест медленно)
5) Общий аппетит (General appetite, GA)	4 (My baby has a strong appetite) / 4 («У моего ребенка сильный аппетит»)	3 ("My baby likes milk") / 3 («Мой ребенок любит молоко»). 4 ("My baby has a strong appetite") / 4 («У моего ребенка сильный аппетит»)

All this makes it doubtful that the Russian version of the Baby Eating Behaviour Questionnaire can be used for its intended purpose, i.e. for psychometric measurement of eating behaviour in children in the first year of life. Unfortunately, unacceptable reliability values of the test scales (consistency of scale items) make meaningless the further stage of the instrument development — the study of convergent, criterion and content validity .

Thus, in the course of the present study, negative results were obtained with regard to the psychometric properties of the studied questionnaire and possible prospects for its use in paediatric practice. The size of the sample used, the calculation of the suitability of the data set, the multicentre and longitudinal nature of the study exclude the random nature of the revealed patterns, which nevertheless dictates the need to critically evaluate the negative results obtained, which, as already mentioned, have a high level of statistical validity.

The Russian-language Baby Eating Behaviour Questionnaire generally explores the sphere of reflexivity of psychological processes underlying the mechanisms of eating behaviour both in the child and in the mother (based on the principle of mirroring the infant's emotions experienced by the mother as a manifestation of attachment relations in the mother-child system). The components of the Russian-language scales revealed in our work indicate the absence of clear semantic patterns in the studied characteristics of baby eating behaviour. They also indicate that mothers lack knowledge about the developing eating habits of their infants.

This was manifested by a low degree of understanding and differentiation by mothers of such nutritional processes of the child as the desire for food (the food craving), the pleasure derived from feeding, the pace of feeding, and the feeling of satiety. For example, such an important phenomenon of infant feeding as "food responsiveness" (the scale of the questionnaire "Desire to eat"), reflecting the presence of food interest, attunement to food, disposition to it, positive reaction to food, turned out to be little realised and undifferentiated by mothers. This is confirmed by the revealed "coupling" of food responsiveness with other food sensations — the feeling of satiation, emotions experienced during feeding, the rate of milk absorption. That is, we are talking about the absence of semantic clear boundaries of the described psychological phenomenon.

It is important to emphasize that the processes underlying the phenomenon of infant overeating and, as a number of studies have shown, overweight children [5, 6, 7], such as impaired eating speed and sensitivity to satiety, were also represented in the proposed version of the questionnaire in a reduced form (the scale "Sensitivity to overeating" included only one of the three items characteristic of the original version, and the scale "Slow eating process" included only two of the four such items). This indicates a lack of maternal tracking of the processes underlying overeating, and hence the relevance of this problem stated in the introduction to this article.

Such a characteristic as "pleasure from eating" was also ambiguously described. The infant's perception of positive emotions associated with feeding was mixed with food cravings (the "Desire to eat" scale). This fact, from our point of view, has a direct relation to the prevalence of eating

disorders in the early childhood population, as it underlies the phenomenon of "somatopsychological differentiation disorder" (somatopsychological differentiation), a fundamental concept of psychosomatics, manifested in the inability to differentiate emotional experiences (anger, irritation, frustration, etc.) and bodily sensations (hunger, satiety, etc.). This mechanism, which is formed and consolidated at the early stages of ontogenesis of eating behaviour, is expressed in such well-known phenomena as "stress eating", when any emotional discomfort at the level of interoceptive awareness is experienced as a feeling of hunger. The emotional mechanisms of development of eating disorders are the most important, according to I. Chatoor, a well-known researcher of children's eating behaviour. According to the well-known researcher of children's eating behavior I. Chatoor, the emotional mechanisms of the development of disorders can already be traced by the example of infantile anorexia, when refusing food helps to involve the mother more deeply in the infant's eating behavior and, thereby, satisfy the child's unrealized need for attention and emotional warmth [12]. One should also take into account the opinion of some domestic researchers that in families of infants with infantile eating disorders there is an overvalued attitude to food intake (a "food cult"), when the child's "satiety" is considered a criterion of physical and mental well-being. Communication between adults and children, both before and after the onset of the disorder, is emotionally impoverished; in these conditions, food is the only "means of communication" between parents and children [13].

In conclusion, it is important to note once again that the predominantly milk-based nature of the child's diet in the first months of life determines, on the one hand, the relative monotony of "food externality", i.e. the insignificant connection of the child's appetite with the type, taste of food, form of presentation, and environment, and, on the other hand, to a much greater extent determines the dependence of the child's eating behaviour on the perceived emotional and sensory patterns emanating from the mother.

One of the indirect conclusions that follow from the presented material is the need for doctors and psychologists to work on cultivating in young parents an interest in observing the mental life of their infants. It is also important to conduct psycho-educational work devoted to the development of knowledge about the peculiarities of children's behaviour and development. In particular, it is necessary to introduce the method of parental reports and diaries of self-observation of infant feeding, which should be considered as objective material for identifying clinical symptoms of disorders, as well as a method of therapy (the method of "food diary"), repeatedly described in the literature [14].

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ROLE OF MODERN DIAGNOSTIC METHODS IN DETERMINING OF SURGICAL TACTICS IN PATIENTS WITH RETROSTERNAL GOITER

© Igor V. Karpatsky, Zoya S. Matveeva, Idris R. Shudaev, Alexey L. Akinchev

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Igor V. Karpatsky — MD, PhD, Associated professor of the Department of Hospital Surgery, General Medical Practice.
E-mail: ikar122@list.ru ORCID: 0000-0003-0047-6327

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Abstract. *Introduction*. Retrosternal goiter is called the location of the thyroid gland partially or completely below the level of the jugular notch of the sternum. Its frequency is in the range 10–15% in the structure of thyroid pathology. *The aim of the study* is to search for factors that can affect the course and volume of surgical intervention in patients with retrosternal goiter. *Material and methods*. The study was performed in a clinic of the Center of Endocrine Surgery, where 1156 operations for various thyroid diseases were performed in 2011–2019. Cervicothoracic goiter was detected in 227 (19.6%) patients. *Results and discussion*. The retrosternal goiter had clinical symptoms depended on the degree of compression of mediastinal and neck organs. Persistent compression contributed to relative compensation and the asymptomatic course in 78 (34.4%) patients. Computed tomography had the leading role in diagnostic. It makes possible to clarify the localization, determine the degree of compression of the neck organs, especially the trachea, and assess the deformation of the mediastinum. The most significant factors for surgical tactics and the likelihood of expanding the volume of the operation were: size of goiter retrosternal part and its relationship with the upper thoracic aperture, localization of the goiter in the anterior or posterior mediastinum, the relations of thyroid tissue with vital organs, large vessels and nerve trunks. Supplementation of cervical access with longitudinal transverse sternotomy was planned in 18 cases, but the real need for it arose only in 2 (0.9%) cases. *Conclusion.* 1. Computed tomography with three-dimensional reconstruction is the most informative diagnostic method for the choice of surgical tactics in patients with retrosternal goiter. 2. Modern software allows qualitative and quantitative analysis of tomograms with the identification of possible risk factors for changes in the volume of intervention. 3. Most patients with retrosternal goiter can be operated on through cervical access. 4. Quantitative spirography assessment could be used to determine the urgency of the intervention.

Key words: *thyroid gland; retrosternal goiter; mediastinum; recurrent goiter; sternotomy; computed tomography*

РОЛЬ СОВРЕМЕННЫХ МЕТОДОВ ДИАГНОСТИКИ В ОПРЕДЕЛЕНИИ ХИРУРГИЧЕСКОЙ ТАКТИКИ У БОЛЬНЫХ ШЕЙНО-ЗАГРУДИННЫМ ЗОБОМ

© Игорь Владимирович Карпатский, Зоя Сергеевна Матвеева, Идрис Рашидбекович Шудаев, Алексей Львович Акинчев

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Игорь Владимирович Карпатский — к.м.н., доцент кафедры госпитальной хирургии, общей медицинской практики.
E-mail: ikar122@list.ru ORCID: 0000-0003-0047-6327

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Резюме. *Введение.* Шейно-загрудинным зобом называют расположение щитовидной железы частично или полностью ниже уровня яремной вырезки грудины. Его частота в структуре тиреоидной патологии составляет 10–15%. Актуальность работы обоснована потребностью в точном определении порядка обследования и тактики хирургического лечения. *Цель исследования:* поиск факторов, способных повлиять на ход и объем хирургического вмешательства у больных загрудинным зобом. *Материалы и методы.* Исследование выполнено в клинике Центра эндокринной хирургии, где в 2011–2019 гг. выполнено 1156 операций по поводу различных заболеваний щитовидной железы. Шейно-загрудинный зоб выявлен у 227 (19,6%) пациентов. *Результаты и обсуждение.* Загрудинный зоб имел клиническую симптоматику, определявшуюся степенью сдавления того или иного органа. Ведущую роль в диагностике играла компьютерная томография, дававшая возможность уточнить локализацию, определить степень компрессии органов шеи, особенно трахеи, оценить деформацию средостения. Наиболее значимыми в определении хирургической тактики и вероятности расширения объема операции оказались: размер загрудинной части зоба и его соотношение с наиболее узким местом — верхней грудной апертурой, локализация зоба в переднем или заднем средостении, взаимоотношение тиреоидной ткани с жизненно важными органами, крупными сосудами и нервными стволами. Дополнение шейного доступа с продольно-поперечной стернотомией планировалось в 18 случаях, однако реальная потребность в нем возникла лишь в 2 (0,9%) наблюдениях. *Выводы.* 1. Наиболее информативным методом диагностики, определяющим вероятный объем и тактику хирургического лечения у больных загрудинным зобом, является компьютерная томография с трехмерной реконструкцией. 2. Современное программное обеспечение позволяет производить качественный и количественный анализ томограмм с определением возможных факторов риска изменения объема вмешательства. 3. Большинство больных загрудинным зобом может быть оперировано через шейный доступ. 4. Для определения срочности вмешательства можно использовать количественную оценку функции внешнего дыхания.

Ключевые слова: *щитовидная железа; загрудинный зоб; средостение; рецидивный зоб; стернотомия; компьютерная томография*

INTRODUCTION

Cervical sternal localisation refers to the location of the thyroid gland partially or completely below the leve notch. In this case, most often a goitrous thyroid tissue, initially located in a typical place, under the influence of gravity and suction action of the thorax is gradually displaced down into the anterior or, less often, posterior mediastinum. Nodular transformation can also be subjected to dystopian thyroid tissue.

There is a steady increase in patients with nodular formations of the thyroid according to WHO data[1, 2]. The frequency of cervicothoracic goiter (CTG) varies widely — from 2.6 to 30.4% and averages 10–15% of all thyroid pathology. This percentage is particularly high in regions endemic for thyroid disease. Primary intrathoracic goitre is much less common and accounts for no more than 1% of all goitres [3]. The share of intrathoracic goiter in the group of mediastinal tumours and cysts is more than 30%, occupying the first place among benign masses of this localisation. Often CTG is a finding in women of the older age group (average age 65 years), and it is extremely rare in young age. The process of thyroid tissue prolapse is facilitated by the absence of fascial partitions, which would limit its movement into the mediastinal space. Another factor causing the anterior spread of goitre is the resistance of the muscles and fascia of the anterior surface of the neck [1, 2, 4–6], which restrain the anterior growth of goitre.

Surgery is the main accepted method of treatment of CTG. Surgical interventions in this category of patients are technically more complicated, as pathologically altered thyroid tissue may extend deep into the mediastinum. The large size of the goiter and the impossibility to mobilise its lower poles without extraction in the cervical access increase the difficulty of visualisation of the recurrent laryngeal nerve and the risk of its trauma, both surgical and traction. Due to the high risk of injury of the inferior thyroid artery with subsequent development of difficultly controlled bleeding into the mediastinum when pulling the lower pole of the thyroid, it is sometimes necessary to perform a combined access: cervical access with longitudinal-transverse sternotomy [1, 3, 7]. Some authors, however, state that all retroperitoneal goitres can be safely removed via cervical access, with the exception of primary intrathoracic goitre and recurrent thyroid cancer [6]. The role of endovideosurgical and video-assisted surgical techniques in patients with tonsillar goiter is limited due to the difficulty in achieving optimal angulation of the instrument [8]. Nevertheless, there are reports on thoracoscopic assisted interventions [9].

AIM

A searching for factors that may influence the choice of access and operative technique in patients with an intrathoracic goiter.

MATERIALS AND METHODS

The study was performed in the clinic of the St. Petersburg Centre for Endocrine Surgery and Oncology on the basis of the St. Petersburg State Budgetary Institution "City Hospital No. 26". 1156 operations for various thyroid diseases were performed here in 2011–2019. Goiter of cervicothoracic localisation was detected in 227 (19.6%) patients. There were 34 (15.0%) men, 193 (85.0%) women. The age of patients in the study group ranged from 18 to 86 years and averaged 61.0±12.8 years, which is about 6 years more than for the general group of patients with thyroid diseases. All patients were hospitalised and operated in euthyroidism. The degree of cervicothoracic location of goiter was determined according to the classification of A.F. Romanchishen (1992) [6]:

I degree — the lower poles of the thyroid lobes tend to extend behind the sternum;

II degree — the lower poles of the thyroid lobes are located retrosternally, but they are brought to the neck at palpation at the moment of swallowing;

III degree — the lower parts of the thyroid located in the sternum are not displayed on the neck during palpation at the moment of swallowing;

IV degree — only the tops of thyroid lobes are palpatorily detected on the neck;

V degree — the whole goitre-altered gland is located in the mediastinum (intrathoracic goiter).

The study included patients with II degree or more of cervicothoracic spread of thyroid tissue, because it has the greatest influence on the tactics and technique of surgical intervention. The number of patients with II degree of cervicothoracic spread of goiter was 30 (13,3%), with III — 156 (68,7%), IV — 38 (16,7%), V degree (intrathoracic location) was revealed in 3 (1,3%) patients. There were no statistically significant differences in the mean age depending on the degree of intrathoracic spread, although the mean age of patients with V degree of retroperitoneal spread was the highest (65.03±5.3 years). All patients underwent a complex pre-operative examination, which included analysis of clinical symptoms, ultrasound of the neck, multispiral computed tomography (MSCT), and the neck scintigraphy if differential diagnostics was necessary.

The primary diagnosis of a hypogastric goiter was based on the analysis of complaints and clinical data. The anterior goitre had clinical symptomatology determined by the degree of compression of organs. Prolonged compression of neck and mediastinal organs contributed to relative compensation and asymptomatic course of the disease, which was masked by concomitant pathology. The most frequent somatic diseases were cardiopulmonary diseases such as bronchial asthma, chronic obstructive pulmonary disease, obesity, atherosclerotic cardiosclerosis. However, decompensation with the manifestation of a visible clinical picture occurred with time. An asymptomatic course of the disease was observed in 78 (34.4%) cases. In these cases, preliminary diagnosis was performed by palpation.

The purpose of in-depth examination, which included an ultrasound and a MSCT, was to search for indications for surgery, to select the surgical access, and to plan the main stage of surgery. The main aim was to clarify the probability of expanding the access to sternotomy.

Taking into account the possibility of asymptomatic course of slowly developing laryngeal paresis, all patients were examined by an otorhinolaryngologist in the preoperative period. Hoarseness of voice can be a sign of compression or sprouting of the recurrent laryngeal nerve by a malignant tumour. The presence of proven laryngeal paresis influences the choice of surgical tactics.

Statistical processing of the obtained data was performed using the Student's criterion.

RESULTS

In our study, the most frequent (17.6%) and clinically significant symptomatology was dyspnoea at the lowest physical load and at the rest, as well as in the supine position, with characteristic stridor (Table 1). As a result, the patients had to sleep on the elevated bed , in a half-sitting position, on the stomach or on the side of the sternal node in case of unilateral thyroid enlargement. The presence of dyspnoea in most cases (87.5%) was combined with cervicothoracic goiter of III–V degree. Patients complained to headache due to impaired venous outflow. Characteristic symptoms were also: the coughing attacks, the signs of dysphagia, the swelling of superficial jugular veins, and, as a consequence, the compression of mediastinal vessels with the development of superior vena cava syndrome.

The majority of patients at the outpatient stage were long-term observed by endocrinologists, pulmonologists, therapists, cardiologists. The follow-up period ranged from 1 to 59 years, on average 10.8±7.2 years. It was maximal in patients with

Table 1. Main complaints in cervicothoracic goitres

Таблица 1. Основные жалобы при шейно-загрудинных зобах

Complaints / Жалобы	A number of patients / Количество пациентов	A frequency of symptoms, % / Частота симптомов, %
Dyspnoea at rest and a feeling of suffocation in a hori-zontal position / Одышка в покое и чувство удушья в горизонтальном положении	40	17,62
Neck deformation / Деформация шеи	50	22,02
Dysphagia / Дисфагия	14	6,16
Feeling of tightness in the neck / Чувство сдавления в области шеи	72	31,71
Swelling of the neck veins / Набухание шейных вен	19	8,37
Voice changes / Изменение голоса	6	2,64
Coughing fits that get worse in a horizontal position / Приступообразный кашель, усиливающийся в горизонтальном положении	11	4,84
Heart rhythm disorders / Нарушения сердечного ритма	1	0,44
Lack of complaints / Отсутствие жалоб	78	34,36

III–IV degree of goiter — 11,3±5,2 years. Excessive concentration of specialists on profile pathology, narrowing of examination spectrum, underestimation of imaging techniques data contributed to diagnostic and tactical mistakes. Unfortunately, as practice has shown, the retroperitoneal goitre, noticeable as an enlargement of the upper mediastinum shadow, was often not described by radiologists in the fluorographic examination conclusions, which led to diagnostic mistakes and unreasonable prolonged observation. Differential diagnosis was complicated by the presence of concomitant severe pathology of the respiratory system in 4 patients.

All patients with suspected compression syndrome underwent a study of external respiratory function (spirography), which made it possible to determine the nature of airway patency disorder and the degree of respiratory insufficiency. These data influenced the tactics of preoperative and postoperative period treatment and allowed to determine the indications for urgent interventions in emergency patients [10]. Incorrect interpretation of clinical data and the contribution of thyroid disease can lead to the aggravation of respiratory disorders in the postoperative period. In complicated cases, the repeated investigations of external respiratory function, ECG and Echocardiography are necessary with further involvement of appropriate specialists.

Ultrasound in cervicothoracic goitre had limited informativeness due to the impossibility to assess the size and structure of the thyroid part located in the mediastinum. It was possible to examine the gland only in patients with II and III degree of subclavian location. Fine-needle aspiration biopsy was performed in all patients with thyroid nodular tumours. The colloid goiter was detected in 85 (55,9%) patients, the follicular tumour in 58 (38,2%) cases, the Hashimoto thyroiditis in 5 (3,3%) patients and the papillary carcinoma in 4 (2,63%) observations. The presence of compression syndrome was an indication for surgical treatment in cases of benign thyroid pathology.

The main method to diagnose cervicothoracic goiter was the X-ray. A MSCT of the chest with contrasting of the vascular system was used for topical diagnosis, determination of the degree of compression and evaluation of the neck and mediastinal organs deformation and clarification of anatomical relationships. The indications were: a cervicothoracic goiter of IV-V degree, a presence of compression syndrome, a suspicion of malignant growth. Magnetic resonance tomography was not used because of less clear visualisation of the sternal goiter.

MSCT helped to answer the main question of preoperative preparation of patients with cervicothoracic goiter about planning of surgery and choice of surgical access. In patients with large retroperitoneal neoplasms there is a risk of supplementing the cervical access with longitudinal-transverse sternotomy. Such interventions required additional preparation not only on the part of the patient, but also on the part of the operating theatre, which consisted in additional coordination of the surgical plan and preparation of instrument sets and consumables.

Based on the conducted survey, all patients were divided into 3 groups depending on the probability of sternotomy access and the features of performing the main stage.

In our experience, the most significant in determining the probability of sternotomy at the preoperative stage were the following features: the size of the anterior part of the goiter and its relationship to the narrowest place — the upper thoracic aperture, localisation of the goiter in the anterior or posterior mediastinum, the relationship of thyroid tissue with vital organs and large vessels and nerve trunks. Combined cervical access with longitudinal-transverse sternotomy was planned in 18 (7.9%) cases, but the real need for it occurred only in 2 (0.9%) observations.

Modern software for DICOM-images analysis allowed easy visualisation of the goitre-altered thyroid in the main projections and performing cross-sections according to the specified parameters. Availability of such programs allowed to widely use a 3D modelling in the course of planning surgical interventions in the last 5 years. The transverse, sagittal and longitudinal dimensions of the sternal part of the goiter were measured and its volume was calculated. The obtained data were compared with the transverse and sagittal dimensions of the bony ring of the upper thoracic aperture. Sternotomy was considered probable if at least one of the maximum dimensions of the goiter in the transverse plane exceeded 2/3 of the corresponding size of the upper thoracic aperture. Additional risk factors were considered to be goitre extension into the posterior mediastinum, deeper than the aortic arch, thyroid tissue dystopia into the mediastinum, recurrent and malignant nature of the disease. The probability of access extension progressively increased when two or more factors were combined.

In one of the two cases in which sternotomy was performed, there was a combination of large size and recurrent goitre with ectopy of the tissue into the mediastinum. In the second case, the patient was operated on for cervicothoracic location of papillary thyroid cancer with metastases to mediastinal lymph nodes.

The following clinical observation demonstrates the risk assessment of sternotomy and surgical tactics. Patient L., 41 years old, was urgently admitted to Hospital No. 26 on 03rd April of 2019. She was transferred from a non-specialised regional clinic, where she was examined for a mediastinal mass detected on the fluorogram in January 2019, the mediastinoscopy with biopsy and the lymph node removal was performed. Fragments of macro-microfollicular goiter, follicular adenoma were found in all micropreparations during histological examination.

The patient knew about the thyroid disease since the age of 16. She was operated in 1994 (the volume is unknown, medical records have been lost). She was not observed by an endocrinologist and was not examined. On admission, she complained of dyspnoea with minimal physical exertion, impaired swallowing of solid food. Examination revealed dilated saphenous veins in the neck. The thyroid gland was inhomogeneous due to dense-elastic nodules, enlarged due to both lobes, partially located in the sternum, it did not protrude to the neck when swallowing. The patient was in euthyroid state. MSCT revealed a picture of a hypervascular volumetric mass of the upper and anterior mediastinum with the presence of a vascular pedicle coming from the posterior-lower edge of the left thyroid lobe (the size was 95×06×149 mm). There were signs of compression, displacement of elements of the vascular bundle and heart. There was the deviation of the trachea and oesophagus to the right (Fig. 1).

The diagnosis was recurrent polynodosis euthyroid goiter of cervical and sternum localisation of the IV degree, with compression and deviation of the neck and mediastinal organs. In the spirogram, the forced expiratory volume in 1 second and peak volume velocity were within normal limits (98 and 95%, respectively). No indications for emergency surgery were found. A decision on urgent surgery was made because of the risk of progression of respiratory disorders. The risk of sternotomy was considered to be extremely high (there was a combination of three factors: size ratio, depth of location, recurrent goitre).

Under endotracheal anaesthesia the patient underwent an access on the anterior surface of the neck with excision of the old postoperative scar. In the course of revision, the right lobe of the thyroid with the size of 5×4×3 cm and the left lobe with the size of 4×4×3 cm were identified from the scars. The tissue was diffusely changed. From the lower pole of the left lobe there was a neoplasm spreading to the anterior mediastinum. The isthmus was absent. The right lobe of the thyroid was mobilised and removed under the control of the recurrent nerve on the right side. The left lobe was partially mobilised, the upper pole of the sternal mass was isolated. The latter was wedged into the upper thoracic aperture, surrounded by large vessels, squeezed and displaced the trachea backwards and to the right. It was impossible to remove the mass through the cervical access, a partial longitudinal-transverse sternotomy up to the third intercostal space was performed. The anterior superior mediastinum was occupied by a large nodular neoplasm 18×15×16 cm connected by a thin cord with the lower pole of the left thy-

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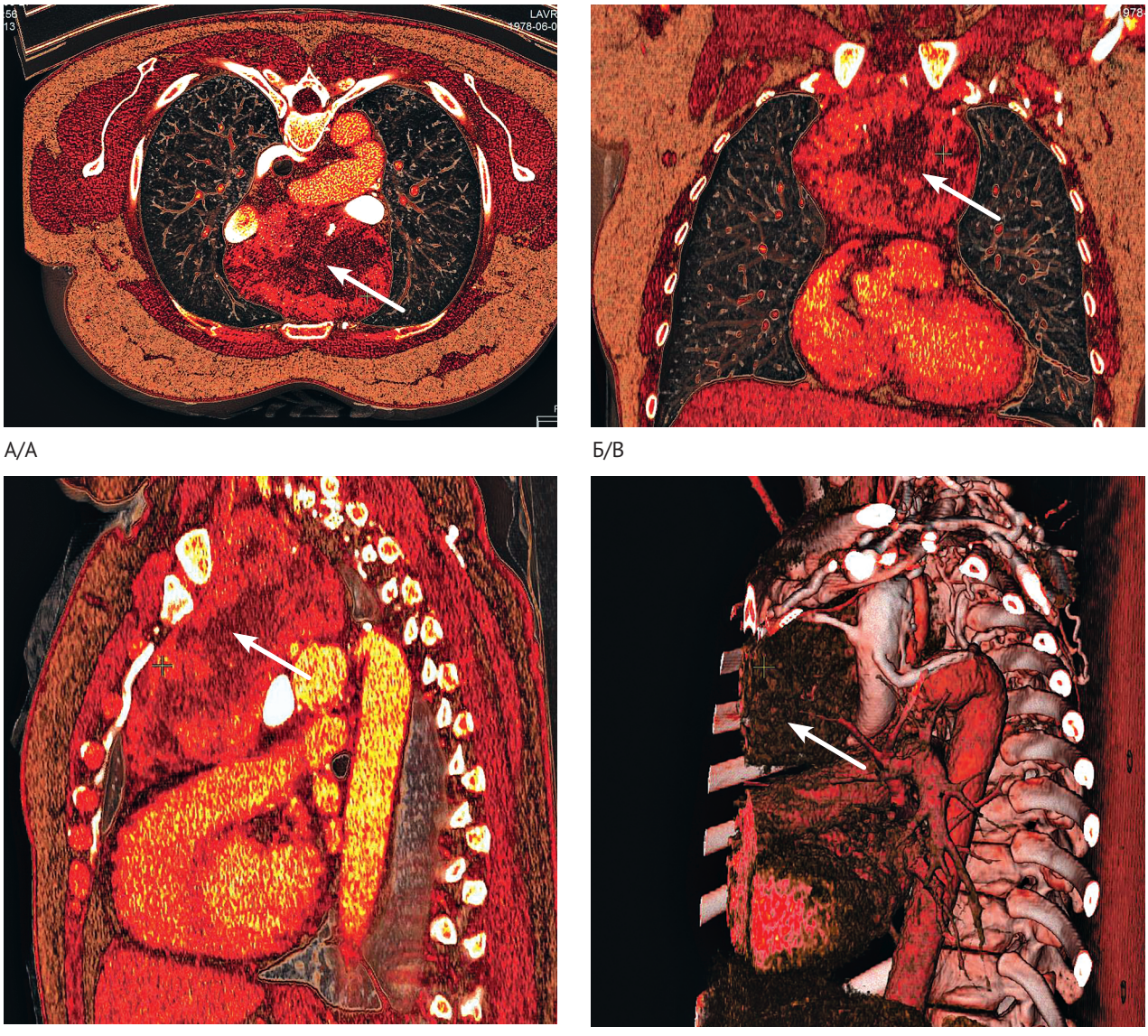


А/A Б/B

В/C Г/D

Fig. 1. Multispiral computed tomography of the neck with intravenous contrast enhancement (mediastinal tumor is indicated by an arrow): A — transverse projection; B — frontal projection; C — sagittal projection; D — three-dimensional reconstruction

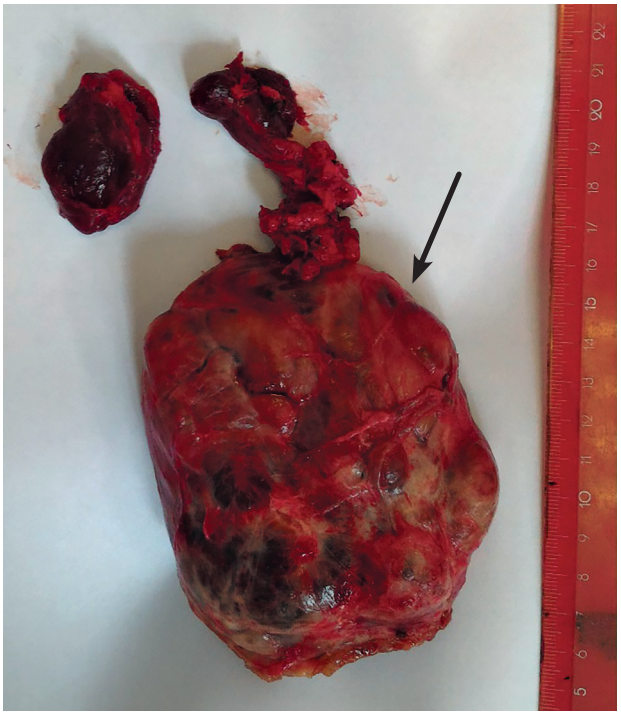
Рис. 1. Мультиспиральная компьютерная томография шеи с внутривенным контрастным усилением (образование средостения указано стрелкой): А — поперечная проекция; Б — фронтальная проекция; В — сагиттальная проекция; Г — трехмерная реконструкция

roid lobe. The neoplasm was mobilised with preservation of the main mediastinal structures and removed (Fig. 2). The postoperative period was smooth, the patient was discharged on the 10th day in satisfactory condition under the supervision of the endocrinologist of the polyclinic. The substitution therapy was prescribed.

Esophagoscopy and fibrobronchoscopy were necessary for patients with large retroperitoneal goitres, especially in case of suspected malignant growth. In patients with compression syndrome, it is advisable to perform them during operation because of the possible risk of progression of respiratory disorders. Intubation of such patients is also performed under bronchoscopy control due to significant displacement and narrowing of the laryngeal and tracheal lumen, which should be warned to the anaesthesiologist in advance.

There were patients who were admitted to the hospital for emergency indications with signs of the respiratory failure and the threat of asphyxia in the group of operated patients. The main task of the surgeon on duty in such a situation was to perform differential diagnosis and determine the role of cervicothoracic goiter in the clinical picture. On the degree of tracheal compression, the need for surgery was based on the urgent or emergency procedure. The study of external respiratory func-

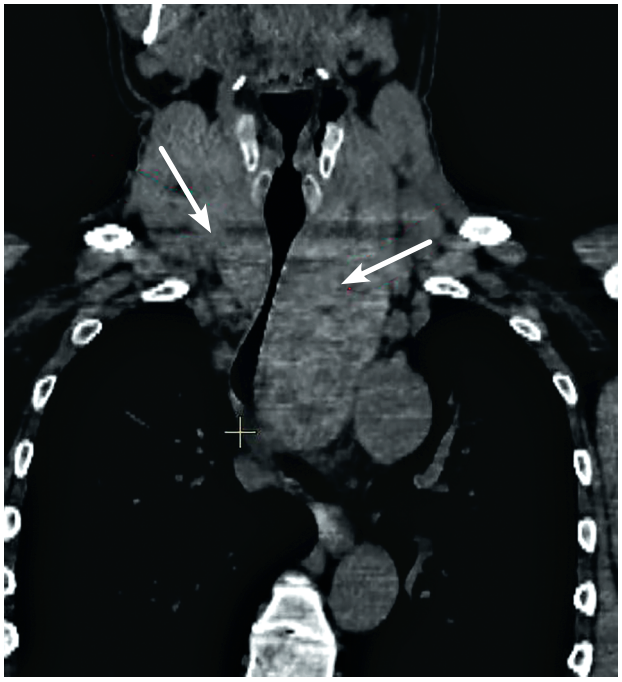
А/A



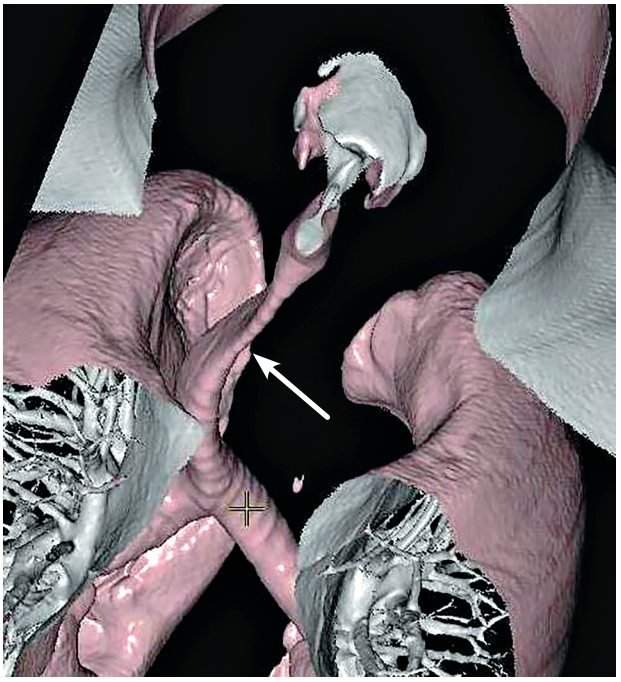
Б/B

Fig. 2. Sternotomy with retrosternal goiter: A — mobilization of mediastinal goiter; B — macroreparation (the mediastinal part is marked by an arrow)

Рис. 2. Стернотомия при загрудинном зобе: А — выделение загрудинного зоба; Б — макропрепарат (загрудинная часть маркирована стрелкой)



А/A



Б/B

Fig. 3. Computed tomogram in direct projection (A); three-dimensional reconstruction of the tracheobronchial tree (B) (stenosed trachea is marked with an arrow)

Рис. 3. Компьютерная томограмма в прямой проекции (А); трехмерная реконструкция трахеобронхиального дерева (Б) (стрелкой отмечена стенозированная трахея)

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tion and MSCT took the leading place in determining the indications for emergency intervention. In modern conditions against the background of the COVID 19 pandemic, the computer tomography is also indispensable for detecting signs of specific pneumonia, because the clinical manifestations in the form of dyspnoea are the same, and combined variants may occur, presenting serious problems in the tactical plan.

A variant of surgical tactics is illustrated by the following clinical observation. Patient S., 49 years old, was admitted on emergency indications with the diagnosis of "acute respiratory infection, respiratory failure". On admission he noted pain in the throat, dyspnoea at minimal physical activity. Examination revealed a sharp neck deformity of a significantly enlarged thyroid. A surgeon was summoned. From the anamnesis it is known that the patient knew about the thyroid disease for about 5 years. He had not been observed by doctors and had not previously asked for medical help. The dyspnoea on physical load started to be noted a year ago. Recently the progressive decrease of tolerance to physical load was noted. Deterioration occurred against the background of catarrhal symptoms. On observation: the neck area was sharply enlarged and deformed due to both lobes of the thyroid, extending up to the hyoid bone and down behind the sternum, there was a dilation of the subcutaneous vein network in the neck area. Acrocyanosis appeared only during physical exertion. The trachea was displaced to the right in the lower neck. Cervical lymph nodes were not palpatorily enlarged.

The patient was examined in the hospital emergency room, the MSCT of the chest with neck involvement was performed. The goiter of cervico-sagittal localisation of IV degree with compression and deviation of neck and mediastinal organs, the subcompensated tracheal stenosis, the left-sided maxillary sinusitis were detected. A mass with clear irregular contours, 8.3×8,6×10,4 cm in size, originating from the left lobe, spreading into the posterior mediastinum, around and beyond the tracheal bifurcation was visualised. The tracheal lumen is narrowed to 4×27 mm. There was compression of mediastinal vessels. The length of the stenosis was 8.7 cm. The structure of the mass was heterogeneous due to the presence of small calcinates (Fig. 3).

In the left lobe there were multiple nodules up to 22 mm, in the right lobe — the lower pole was represented by a nodule 43×33 mm. The study of external respiratory function revealed a significant decrease in forced expiratory volume in 1 second (45% of the norm), Tiffno index (65% of the norm), peak expiratory volume velocity (26% of the norm).

Taking into account the spirography data (the forced expiratory volume was 45%), the tactical approach patented by our collective [10], the absence of dyspnoea at rest, it was decided to prepare the patient for urgent surgery. The patient was given oxygen through nasal catheters. The treatment of maxillary sinusitis was started with the help of otorhinolaryngologist. There was V according to the results of thyroid function study. After inflammatory phenomena control on the 4th day the patient underwent surgical treatment to eliminate compression of neck organs and mediastinum. Taking into account the spread of the goiter to the level of the main bronchi, despite the fact that its transverse size did not exceed 2/3 of the size of the upper thoracic aperture, the probability of sternotomy access was taken into account at the stage of planning the operation.

The patient's thyroid was exposed layer by layer using the Kocher access under an endotracheal anaesthesia (an intubation with a bronchoscope). Subcutaneous veins are considerably dilated. At revision both thyroid lobes were sharply enlarged (right 12×6×5 cm, left 18×8×6 cm). Their lower poles went behind the sternum into the posterior mediastinum, annularly covered and squeezed the trachea and oesophagus, the tissue was diffusely changed due to multiple nodules of colloid structure. After ligation of the upper and lower thyroid vessels, the thyroid tissue decreased in size, which allowed its removal from the sternum to the cervical access. Thyroidectomy was performed under the control of the recurrent laryngeal nerves and perithyroid glands.

The postoperative period was normal. The patient was discharged for outpatient treatment on the 5th day after surgery. Histological conclusion was diffuse nodular macro-microfollicular colloid goiter. At the control check-up in a month the patient felt well, respiratory insufficiency was eliminated, he was physically active and had no complaints. Control spirography in 6 months showed the recovery of respiratory function.

It was possible to stabilise the condition of all emergency patients and to perform interventions after preparation with the intensive therapy. 19 (8.4%) patients were operated on urgently, the remaining 208 (91.6%) were admitted as planned. In 13 (5,7%) out of 227 patients goitre was recurrent. The operation of choice in patients with cervicothoracic goiter was thyroidectomy performed in 183 (80.6%) patients. Hemithyroidectomy was performed in 28 (12,3%) patients, and subtotal re-

section was performed only in 3 (1,3%) cases. The operation of choice in case of retroperitoneal recurrent goitre was repeated resection in the volume of thyroidectomy. One (0.45%) patient underwent decompressive resection of the thyroid tumour and in 1 (0.4%) patient palliative removal of the mediastinal tumour was performed.

Intraoperative signs of compression syndrome were detected in 112 (49.3%) patients. Instrumentally its presence was proved only in 41 (18.1%) patients. Tracheal compression and deviation were the most frequent — 103 (92.0%) cases, oesophagus was compressed less frequently — 32 (28.5%) cases, neck and mediastinal vessels — 19 (16.9%) cases. Compression usually occurred at the level of the upper thoracic aperture, which is associated with the presence of a dense bony ring.

Most often (204 (89.9%) observations) the anterior part of the thyroid was located in the anterior mediastinum and only in 23 (10.13%) cases in the posterior mediastinum. Devascularisation of the thyroid tissue during surgical interventions resulted in its volume reduction due to decreased blood flow. This helped to remove it from the sternum to the cervical access, which was achieved in 225 (99.1%) cases. It is necessary to avoid rough traction of thyroid tissue in the cranial direction, as it can lead to rupture of venous plexuses and even tear off the anterior part of the thyroid with the development of massive bleeding into the mediastinum. This will inevitably lead to the need for sternotomy in order to haemostasis. It is also necessary to remember that the introduction of thyroid tissue into the tracheo-esophageal furrow, displacement of the trachea and oesophagus change anatomical relationships in the area of surgery, and the recurrent laryngeal nerves may appear in a completely unexpected place, even on the anterolateral surface of the tumour nodule.

The analysis of immediate results of surgical treatment of 227 patients operated on for cervicothoracic goiter showed that one- and bilateral laryngeal paresis of accidental or forced (in case of nerve sprouting by the tumour) character was present in 2 (0,9%) observations. Postoperative haemorrhages requiring repeated intervention in the early postoperative period developed in 4 (1.8%) patients. These figures are comparable with those in the general group and the literature data [11].

CONCLUSIONS

1. Computed tomography with 3D reconstruction is the most informative diagnostic method determining the probable volume and tactics of surgical treatment in patients with retroperitoneal goitre.

2. Modern software allows to perform qualitative and quantitative analysis of tomograms with determination of possible risk factors for changing the volume of intervention.

3. The majority of patients with a sternal goitre can be operated through the cervical access. A combination of risk factors increases the probability of widening the access: an exceeding at least one of the maximum goitre size in the transverse plane 2/3 of the corresponding size of the upper thoracic aperture, goitre spread to the posterior mediastinum, deeper than the aortic arch, thyroid tissue dystopiated in the mediastinum, recurrent and malignant nature of the disease. The surgeon should anticipate the possibility of sternotomy and has to be prepared to perform it if necessary.

4. Quantitative assessment of external respiratory function can be used to determine the urgency of intervention. If the forced expiratory volume is less than 35% of normal, urgent intervention is indicated.

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 the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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THE METHOD OF STOPPING PROLONGED LACTATION

© Maria V. Gmoshinskaya, Irina V. Aleshina

Federal Research Center of Nutrition, Biotechnology and Food Safity. Ust'inskiy proyezd, 2/14, Moscow, Russian Federation, 109240

Contact information:
Maria V. Gmoshinskaya — Doctor of Medical Sciences, Leading Researcher, Laboratory of Age-Related Nutrition.
E-mail: mgmosh@yandex.ru ORCID: 0000-0002-9932-4720

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Abstract. *Relevance*. When breastfeeding is stopped, an affective attachment to the mother is often noted. In order to solve this problem, a method of gentle cessation of lactation was developed. The basis of the method is objective activity with children older than six months and the beginning of co-creation of mother and child, which contributes to the "emotional restructuring" of the mother, and has an important impact during the period of weaning the child. *Aim*. Development of a method of careful cessation of lactation, which does not have a psycho-traumatic effect on the "mother–child" dyad. *Materials and methods*. Co-creation of mother and child — the method of "infant drawing" (not a method of teaching drawing). Under observation were 47 pairs of "mother–child", who began joint creativity from 6–8 months of a child's life and 30 breastfeeding mothers who want to stop lactation but have psychological difficulties in stopping it. *Results.* A technique has been developed for stopping ongoing breastfeeding, which does not have a psycho-traumatic effect on the "mother–child" dyad. The technique involves the development of contact between mother and child through co-creation, helps to relieve stress in mothers and children during weaning. *Conclusions.* In this situation, co-creation plays the role of a distracting factor that contributes to the transition from communication between mother and child in the process of breastfeeding to communication through creativity, and the earlier it is started (in the first year of life), the higher its effectiveness.

Key words: *continued breastfeeding; lactation cessation; co-creation of mother and child*

МЕТОДИКА ПРЕКРАЩЕНИЯ ДЛИТЕЛЬНОЙ ЛАКТАЦИИ

© Мария Владимировна Гмошинская, Ирина Владимировна Алешина

Федеральный исследовательский центр питания, биотехнологии и безопасности пищи. 109240, г. Москва, Устьинский проезд, 2/14

Контактная информация:
Мария Владимировна Гмошинская — д.м.н., ведущий научный сотрудник лаборатории возрастной нутрициологии.
E-mail: mgmosh@yandex.ru ORCID: 0000-0002-9932-4720

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Резюме. *Актуальность*. При прекращении грудного вскармливания часто отмечается аффективная привязанность к матери. С целью разрешения данной проблемы был разработан метод бережного прекращения лактации. Основу метода составляет предметная деятельность с детьми старше шести месяцев и начало сотворчества матери и ребенка, что способствует «эмоциональной перестройке» матери и оказывает важное влияние в период отлучения ребенка от груди. *Цель*. Разработка методики бережного прекращения лактации, не оказывающей психотравмирующего влияния на диаду «мать–ребенок». *Материалы и методы*. Сотворчество матери и ребенка — методика «младенческого рисования» (не является методикой обучения рисованию). Под наблюдением находилось 47 пар «мать–ребенок», начавших совместное творчество с 6–8 месяцев жизни ребенка, и 30 кормящих матерей, желающих прекратить лактацию, но имеющих психологические трудности в ее прекращении. *Результаты.* Разработана методика прекращения продолжающегося грудного вскармливания, не оказывающая психотравмирующего влияния на диаду «мать–ребенок». Методика предполагает развитие контакта матери и ребенка посредством сотворчества,

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помогает снятию стресса у матерей и детей при отлучении от груди. *Выводы*. В данной ситуации сотворчество играет роль отвлекающего фактора, способствующего переходу от общения матери и ребенка в процессе кормления ребенка грудью к общению через творчество, причем чем раньше оно начато (на первом году жизни), тем выше ее эффективность.

***Ключевые слова*:** *продолжающееся грудное вскармливание; прекращение лактации; сотворчество матери и ребенка*

The efforts of doctors are aimed to support and prevent breastfeeding during the first 1.5–2 years of life [1]. However, stopping breastfeeding is inevitable. There are different ways to stop lactation. Medicinal cessation of lactation is recommended when the mother lacks milk, but both the mother and the infant are not ready for weaning, and the infant needs psychological help. For this purpose, a method of careful cessation of lactation was developed in consort with psychologists.

MATERIALS AND METHODS

The method was based on the possibility of objective activity and the beginning of co-creation of mother and child. As a result, an "emotional restructuring" of the woman occurs, which is very important during the weaning period. This technique of "infant drawing" is not a method for teaching drawing. It involves the development of contact through co-creation. This technique was created to relieve stress in the mother-child dyad during weaning.

RESULTS OF THE STUDY AND DISCUSSION

The situations in which the developed method of stopping prolonged lactation was used are as follows:

1) psychological difficulties when stopping lactation;
2) repeat pregnancy;
3) stopping lactation for medical reasons;
4) the mother considers the duration of lactation sufficient.

Weaning was not recommended for:

1) acute illness of a child;
2) during preventive vaccinations;
3) in the summer period;
4) when moving a child to another climatic zone.

Before the start of classes, the mother and child consulted a psychologist, but in all cases the breastfeeding mother herself made the final decision on the need to stop lactation. If there was an affective attachment to the mother in a child over one and a half years old, psychological preparation was carried out not only for the mother, but also for the child. The conversation with the child was conducted in a playful way. Before the beginning of classes, mothers attended a 4-hour seminar, which consisted of theoretical and practical parts. At the seminar, parents get acquainted with the aims and objectives of this methodology and the technology for its implementation. Much attention is paid to safe art materials. The seminar is accompanied by a video and presentation. Parents were given the opportunity to become familiar with infant drawing techniques in practice. After the seminar, parents began attending classes with their children. Frequency of sessions: 2–3 times a week. "Infant drawing" creates a favorable background for stopping prolonged lactation. The main condition is that the process of "infant drawing" arouses interest in the child's mother.

The developed technique was used to stop prolonged lactation in 30 breastfeeding mothers who wanted to stop lactation, but had psychological difficulties in stopping it. The work was carried out in a group of short-term stays of children with their mothers.

The process of cessation of lactation itself consists of two stages.

1. The preparatory stage, when a mother psychologically prepares for the cessation of lactation. The duration of this period ranged from several days to several months.
2. The stage of actually stopping a baby from attaching to the breast. The duration of this stage is 1–3 days, provided the psychological readiness of the mother-child dyad.

The novelty of this study lies in the fact that we proposed a methodology for joint activity of a mother and child when they participate together in the creative process.

Mother's role:

1. The mother participates with her emotional support, showing interest in what the child is doing.
2. You should not draw instead of a child. If the mother wants to draw, she can draw on a separate sheet, the child will imitate her.
3. The teaching role of the mother: to introduce the child to a material (paint, paper), to show various "drawing" techniques.

4. The mother communicates with the child in the process of the activity.
5. The presence of the mother creates a sense of freedom and security in the child. This has an even greater impact on the development of their contact and mutual understanding. Co-creation is seen as a way of communication.

The developed method for establishing creative contact between mother and child, starting from the first year of life, was used in a group of mothers whose children were breastfed. This study was conducted in a group of short-term stays of a child of the first or second year of life together with his mother. Along with special classes — music, physical education — conditions were created for joint play and creative activity. A special technique "Creativity from infancy" has been developed, which allows to enter into creative contact. The created environment and the conducted classes made it possible to identify the interest of mothers in joint activities and emotional manifestations in them in relation to the child. From among the children attending pre-school institutions, a group of 91 children was identified who had been breastfed for over a year. The children were divided into two groups depending on the start of classes: the first group consisted of 47 mothers and children who began joint creativity from 6–8 months of the child's life, the second group consisted of 44 mothers and children who began joint creativity with their mothers in the second year of life. The frequency of attendance was 2–3 times a week. At home, parents held classes with children independently. The main criterion for assessing effectiveness is the frequency of occurrence of psychological difficulties on the part of the mother or child during the period of cessation of lactation.

The average period for cessation of lactation was approximately the same in both groups and amounted to 16,0±0,7 months in the first and 18,1±0,9 months in the second group, respectively ($P > 0,1$). Difficulties in stopping lactation occurred in 6 (12,8%) children of the first group and 16 (44%) children of the second group ($P = 0,01$).

CONCLUSION

In the situation of weaning, co-creativity plays the role of a distracting factor, facilitating the transition from communication between mother and child in the process of breastfeeding to communication through creativity, and the earlier it starts (in the first year of life), the higher its effectiveness.

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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COMORBIDITY AS A MANIFESTATION OF CONNECTIVE TISSUE DYSPLASIA (CLINICAL CASE DESCRIPTION AND COMMENT)

© Natalia N. Smirnova, Elena I. Zhestyannikova, Valentina N. Belozertseva

Pavlov First Saint Petersburg State Medical University. Ul. L'va Tolstogo, 6–8, Saint Petersburg, Russian Federation, 197022

Contact information:
Natalia N. Smirnova — Doctor of Medical Sciences, Professor, Head of the Department of Pediatrics. E-mail: nephro-uro-kids@mail.ru
ORCID: 0000-0002-0581-7285

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Abstract. An extract from the medical history of a 17-year-old teenager with comorbidity is given — pathology of 4 systems, including the digestive, excretory, immune and nervous systems. An attempt was made to find a common link in pathogenesis — the failure of mesenchymal tissue. An additional survey plan has been proposed to confirm this hypothesis. The need for a joint examination of children with comorbid pathology by a group of specialists of the relevant profiles is justified.

Key words*: comorbidity; mesenchymal tissue; digestive organs; urinary system; immunity; nervous system*

КОМОРБИДНОСТЬ КАК ПРОЯВЛЕНИЕ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ (ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ И КОММЕНТАРИЙ)

© Наталья Николаевна Смирнова, Елена Ивановна Жестянникова, Валентина Николаевна Белозерцева

Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова.
197022, Санкт-Петербург, ул. Льва Толстого, 6–8

Контактная информация:
Наталья Николаевна Смирнова — д.м.н., профессор, заведующая кафедрой педиатрии. E-mail: nephro-uro-kids@mail.ru
ORCID: 0000-0002-0581-7285

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Резюме. Приведена выписка из истории болезни 17-летнего подростка с коморбидностью — патологией 4 систем, включая пищеварительную, выделительную, иммунную и нервную системы. Сделана попытка найти общее звено патогенеза — несостоятельность мезенхимальной ткани. Предложен план дополнительного обследования для подтверждения этой гипотезы. Обоснована необходимость совместного обследования детей с коморбидной патологией группой специалистов соответствующих профилей.

Ключевые слова*: коморбидность; мезенхимальная ткань; органы пищеварения; мочевыделительная система; иммунитет; нервная система*

The term comorbidity was proposed in 1970 by the American doctor A.R. Feinstein. There is no generally accepted international classification of combined diseases.

Several definitions of this clinical concept have been proposed. Comorbidity is a combination of two or more distinct diseases or syndromes, none of which is a complication of the other, if the frequency of this combination exceeds the probability of a random coincidence. Comorbidity is acute and chronic diseases that are not associated with the diagnosis of the underlying disease that was

the reason for hospitalization [1]. The article published in 2018 by L.B. Lazebnik and Yu.V. Konev proposes to use the following classification criteria: genetic predisposition, localization, type and time of occurrence, gender characteristics, disease profile, social causes, comorbid status, localization, etiology and pathogenesis [2].

In pediatric practice, the most common combinations of pathologies of the heart and kidneys (cardiorenal syndrome) is a combination of diseases of the urinary and digestive systems. Pathology of the respiratory system ranks first in frequency in young children. The narrow specialization adopted in modern medicine, including pediatrics, on the one hand, and the lack of erudition of family physicians (general practitioners), on the other, do not allow us to identify the main pathogenetic link of combined pathology, and therefore, to affect it, preventing progression of diseases. One of these links, often is not taken into account in practice, is the inferiority of mesenchymal tissue, or connective tissue dysplasia.

The following extract from the case history, in our opinion, serves as an illustration of this thesis.

17-year-old adolescent

Main diagnosis: (ICD 10: N13.7) reflux nephropathy. Bilateral vesicoureteral reflux (VUR) grade 2 in anamnesis. Endoscopic correction (EC) of ureterovesical anastomosis (UVA) repeatedly (2 g 9 months and 3 g 11 months); chronic kidney disease (CKD) G1A1. Secondary chronic pyelonephritis, remission period.

Associated diagnoses: primary exogenous constitutional obesity; allergic rhinitis, persistent course; pollinosis; type 2 hiatal hernia; reflux esophagitis.

Family anamnesis: mother has type 2 diabetes mellitus, hypertension, obesity, urolithiasis, allergy, pancreatic cancer.

Anamnesis vitae: the boy was born from the 1st pregnancy with the development edema and pyelonephritis; caesarean delivery section was done at 40 weeks. At birth, body weight was 4450 g, length — 55 cm, Apgar score 8/8. Breastfeeding was up to 9 months; excessive weight gain formed from age 12. At the age of 12, allergic bronchitis, allergic rhinitis and pollinosis were diagnosed; at 7 years old, diagnosis: "acute polyradiculoneuritis; lower extremity paraparesis" was done.

Anamnesis morbi: "unmotivated" rises in temperature from 9 months. The first examination by urologist was at 2 years 9 months — bilateral VUR, secondary contracted left kidney; chronic pyelonephritis. Repeated EC UVA at 2 years 9 months and at 3 years 11 months.

State of the urinary system: computed tomography (CT) of the abdominal organs (14 years): left kidney (RS) — 3,1×4,8×7,8 cm; 17 years old: 0,92×0,38 cm, pyelectasia, dilatation of the ureter. Right kidney (RD) (14 years) — 4,8×6,2×10 cm; 17 years old: 1,28×0,52 cm.

Dynamic renal scintigraphy (14 years): severe disturbances in secretory and excretory functions of RS; renal index 29,1%; RD — moderate; renal index 70,1%; transport of the radiopharmaceutical is slowed down on both sides. The last exacerbation of pyelonephritis occurred at the age of 12.

Increases in blood pressure — from 14 years of age (max. 145/98).

Blood biochemistry test: blood creatinine 82 μmol/l; GFR (Schwartz) 135,2 ml/min/1,73 m^2.

Urine: specific gravity 1,007–1,020; albumin 29,3 mg/l; albuminuria 61,17/24 hours.

State of the digestive system: Ultrasound — signs of hepatomegaly with fatty infiltration, biliary dyskinesia, reactive changes in the liver and pancreas.

Fibrogastroduodenoscopy: type 2 hiatal hernia, grade A reflux esophagitis; HP+ gastritis. Fasting glucose level 5,16 mmol/l; HOMA-IR = 2,97 (normal).

Four systems are involved in the pathological process: the nervous system, organs of the urinary system, digestive system, and immune system (allergosis). The concept of the patient dictates the search for a single link in pathogenesis. We hypothesized that connective tissue dysplasia may be a basis for this comorbidity. Connective tissue dysplasia (CTD) is a genetically determined condition characterized by defects in the fibrous structures and ground substance of connective tissue, leading to impaired of the formation of organs and systems. CTD has a progredient course, which defines the features of the related pathology, as well as the pharmacokinetics and pharmacodynamics of drugs [3].

In a 17-year-old adolescent, 4 systems are involved in the pathology:

- urinary system pathology — VUR, complicated by reflux nephropathy and pyelonephritis;
- digestive system pathology — hiatal hernia and reflux esophagitis;
- signs of CTD of the nervous system — disorders of the autonomic nervous system; dysplastic polyneuropathy — polyradiculoneuritis, lower extremity paraparesis;
- disorders of the immune system — allergic bronchitis, allergic rhinitis, persistent course.

This comorbidity suggests the presence of one cause — failure of mesenchymal tissue, or undifferentiated connective tissue dysplasia (CTD).

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To confirm this assumption, it is necessary to supplement the examination with the following methods: family anamnesis and characteristic complaints; biochemical parameters; morphological diagnostics; dermatoglyphics.

The pedigree often reveals comorbidity in pathology of the heart, kidneys, pathology of the gastrointestinal tract, and excessive joint mobility. The most typical patient complaints are fatigue, weather sensitivity, cardialgia, and dizziness.

Basic laboratory diagnostics include a complete blood count, urinalysis, biochemical parameters of acute phase reactions, protein, fat, carbohydrate metabolism, micro- and macro-elements. It is most promising to study metabolites of connective tissue in blood serum, saliva and gastric juice for biochemical confirmation of CTD. The most important parameters during collagen breakdown in tissues are hydroxyprolines (HYP); the level of free HYP is a marker of collagen degradation; HYP-containing peptide reflects both the processes of collagen synthesis and degradation. Glycosaminoglycans, as well as fractions of sialic acids, fucose, and mannose, can serve as markers of proteoglycan degradation and the state of both collagen and glycoprotein metabolism in CTD.

Morphological diagnostics in pediatric practice involves non-invasive methods. Bone densitometry in CTD reveals a decrease in mineralization in flat and tubular bones. One of the most reliable evidence of the presence of CTD is the identification of changes in tooth enamel from childhood. Enamel prisms are the main structural and functional units of enamel, passing in bundles through its entire thickness radially and slightly curved in the shape of the letter S. Based on the results of a study of the ultrastructure of dental enamel, we can talk about a disturbance of the mineralization and organization of enamel prisms in persons with signs of CTD. This is explained by the insufficient packing density of enamel prisms per unit volume, their chaotic arrangement, and insufficient organized and mineralized matrix [4].

Dermatoglyphics, as a method of human genetic research, contributes to the diagnosis of CTD. Sections of dermatoglyphics: fingerprinting — the study of patterns on the pads of the fingers, and plantoscopy — the study of dermatoglyphics of the plantar surface of the foot. With undifferentiated CTD, the development of pachydermodactyly (from the Greek *pachy* — thick, dense, hard) is possible. Morphological changes in pachydermodactyly are characterized by hyperkeratosis, acanthosis, increased dermis thickness, expressed in varying degrees by fibroblast proliferation, and sometimes mucin deposits. An immunohistochemical study of the dermis reveals an increased amounts of types III and V collagen [5].

Indications for genetic counseling confirming/rejecting CTD:

- established or suspected hereditary disease in the family;
- the birth of a child with a congenital malformation;
- physical development delay or mental retardation in a child;
- recurrent spontaneous abortions, miscarriages, stillbirths;
- pathology detection during screening programs;
- consanguineous marriages;
- exposure to known or possible teratogens during the first 3 months of pregnancy;
- unfavorable pregnancy.

The principles for treating CTD are presented in detail in the National Guidelines [3]. The special importance of informing the patient and his parents (legal representatives) about the concept of "CTD", as well as the need for an individual approach to each clinical case, is emphasized. General recommendations include advice on physical activity and a balanced diet. It is necessary to choose the right type of physical activity, adequate load and pace of training. In addition to morning exercises, it is necessary to perform aerobic exercise 3 times a week for 40–60 minutes (swimming, walking or moderate running on a treadmill, cycling/stationary biking, skiing in winter, badminton, bowling, table tennis). Such types of training loads as choreography, team sports with a high probability of injury, weightlifting, as well as chess and piano playing are not recommended due to prolonged static loads (sitting position). High-protein foods containing significant amounts of chondroitin sulfates are recommended. All patients with CTD are recommended to consume products fortified with substances involved in connective tissue metabolism — vitamins C, E, B6, D, P and microelements: magnesium, copper, manganese, zinc, calcium, selenium, sulfur.

CONCLUSION

Comorbidity in pediatrics is an insufficiently studied phenomenon. A patient diagnosed with two or more types of pathology should be observed by a team of specialists. In this case, it is necessary to find a common link in pathogenesis. In addition to mesenchymal deficiency, conditions such as endothelial dysfunction, undiagnosed poly-deficiency conditions, and genetic abnormali-

ties are possible. It is planned to develop reliable markers for different types of comorbidity in children.

ADDITIONAL INFORMATION

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

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CLINICAL CASE OF CARDIORESPIRATORY MONITORING TO CONTROL SUPPLEMENTAL OXYGEN THERAPY IN A PREMATURE BABY

© Anna Yu. Trapeznikova, Dmitry O. Ivanov

Saint Petersburg State Pediatric Medical University. Lithuania 2, Saint Petersburg, Russian Federation, 194100

Contact information:
Anna Yu. Trapeznikova— MD, PhD; Department of Propedeutics of Childhood Diseases with a course of general childcare.
E-mail: anka.solomaha@yandex.ru ORCID: 0000-0003-4461-4322

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Summary. One of the most common respiratory pathologies in infants born prematurely is bronchopulmonary dysplasia (BPD). Pulmonary hypertension is considered a formidable and difficult to diagnose complication of BPD. Maintaining the proper level of oxygen saturation is an integral part of nursing such patients. Cardiorespiratory monitoring (CRM) is performed to record respiratory pauses and episodes of desaturation during sleep. The article discusses a clinical case of cardiorespiratory monitoring to control additional oxygen therapy in a premature infant suffering from bronchopulmonary dysplasia and BPD-associated pulmonary hypertension.

КЛИНИЧЕСКИЙ СЛУЧАЙ ПРИМЕНЕНИЯ КАРДИОРЕСПИРАТОРНОГО МОНИТОРИРОВАНИЯ ДЛЯ КОНТРОЛЯ ДОПОЛНИТЕЛЬНОЙ КИСЛОРОДОТЕРАПИИ У НЕДОНОШЕННОГО РЕБЕНКА

© Анна Юрьевна Трапезникова, Дмитрий Олегович Иванов

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация:
Анна Юрьевна Трапезникова — к.м.н., ассистент; кафедра пропедевтики детских болезней с курсом общего ухода за детьми.
E-mail: anka.solomaha@yandex.ru ORCID: 0000-0003-4461-4322

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Резюме. Одной из наиболее часто встречающихся патологий респираторного тракта у детей, родившихся недоношенными, является бронхолегочная дисплазия (БЛД). Грозным и трудно диагностируемым осложнением БЛД считается легочная гипертензия. Поддержание должного уровня сатурации кислорода является неотъемлемой частью выхаживания таких пациентов. Для регистрации дыхательных пауз и эпизодов десатурации во время сна проводят кардиореспираторное мониторирование (КРМ). В статье рассматривается клинический случай применения кардиореспираторного мониторирования для контроля дополнительной кислородотерапии у недоношенного ребенка, страдающего бронхолегочной дисплазией и БЛД-ассоциированной легочной гипертензией.

Ключевые слова: недоношенный ребенок; апноэ; кардиореспираторное мониторирование

Key words: *premature infant; apnea; cardiorespiratory monitoring*

INTRODUCTION

Currently, preterm birth is a serious problem that contributes to a significant increase in morbidity and mortality all around the world. Complications that arise from preterm birth are the main causes of neonatal mortality [1].

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory pathology in pre-

mature infants, and in 45% of cases it occurs in children with small gestational age and extremely low birth weight who have suffered respiratory distress syndrome and perinatal infections [2]. Exposure to invasive measures that damage lung tissue for a long time leads to long-term persistence of changes in lung structures, including alternating areas of hyper-expansion and atelectasis, fibrosis of the alveolar septum of varying severity, fibrosis of the bronchial submucosa, muscle hyperplasia and the development of pulmonary hypertension [3].

However, lung parenchyma damage is not the only cause of the formation of bronchopulmonary dysplasia. At present, there is a growing understanding of the contribution of growth impairment and remodeling of pulmonary vessels to the development of this pathology. Vascular changes can lead to elevated pulmonary vascular resistance and pulmonary pressure, which in turn promotes the development of compensatory right ventricular hypertrophy and the appearance of clinical signs of pulmonary hypertension (PH).

Immaturity of respiratory control, artificial lung ventilation (ALV) using an endotracheal tube, leading to the development of inflammation and, as a result, narrowing of the upper airways, predisposition to obstruction and small airway luminal diameter, characteristic of preterm infants, as well as lung volume reduction and hypoventilation can lead to low ventilation-perfusion and intrapulmonary adaptability, causing a rapid decrease in oxygen saturation, and contribute to the occurrence of episodes of intermittent hypoxemia and frequent fluctuations in oxygenation [4, 5]. Most are corrected by increasing the fraction of inspired oxygen (FiO2), resulting in some degree of hyperoxaemia. This makes it difficult to maintain SpO_2 within the target range (≥92% for preterm infants with BPD and 94–95% or more [6] for premature infants with BPD-associated pulmonary hypertension), and newborns may spend significant periods of time with SpO_2 below or above target values, which requires constant monitoring for the purpose of timely correction. To improve growth, reduce the severity of symptoms of pulmonary hypertension and the risk of sudden death associated with hypoxemia, constant maintenance of an adequate level of oxygen saturation is required in preterm infants with BPD and BPD-associated pulmonary hypertension [4, 7].

Polysomnography (PSG) and cardiorespiratory monitoring (CRM) are used as objective methods for recording respiratory pauses and short-term desaturation episodes. The use of PSG in newborns and children during the first three years of life is difficult. The use of CRM is acceptable for this category of patients. Infants with BPD may have normal oxygen saturation and respiratory rate during outpatient clinic visits while awake, but they are prone to episodes of desaturation during sleep, along with disordered breathing during the night [8, 9].

CLINICAL CASE

Baby E. was born from the first pregnancy, first delivery. The mother is 36 years old (elderly primigravida), with a burdened obstetric and gynecological anamnesis (chronic endocervicitis). Somatic diseases in the mother: hypotension, polyposis of the gastrointestinal tract, varicose veins of the lower extremities, external hemorrhoids in remission, chronic gastroduodenitis in remission. Occupational hazards, smoking denies.

The delivery was first, premature, at 25 1/7 weeks. Features of the course of labor were breech presentation of the fetus, premature rupture of membranes (anhydrous interval was 9 days), anhydramnios, and chorioamnionitis. At 14 weeks of gestation, the mother's blood was found to be Rh-negative without the presence of antibodies.

The birth weight of the baby was 700 g, body length — 27 cm, head circumference — 22 cm, chest circumference — 21 cm. Apgar scores 1 and 5 minutes after birth were 6 and 7 points, respectively. The condition at birth was assessed as severe due to the development of respiratory failure and extreme morpho-functional immaturity. From birth, the girl was on non-invasive ventilation (NIV), later transferred to nasal CPAP (NCPAP) mode, and was oxygenated satisfactorily. On the 23rd day of life (28 2/7 weeks of postconceptional age, PCA), a worsening condition was noted in the form of increased respiratory failure, deterioration of the clinical picture of the gastrointestinal tract (elements of altered blood were noted on the orogastric tube), manifestations of convulsive syndrome, caused by the implementation of a generalized infectious process with damage to lungs and gastrointestinal tract against the background of deep morpho-functional immaturity. She was transferred to mechanical ventilation with moderate parameters, after 10 days (33rd day of life) she was extubated and transferred to NIV, after 16 days (49th day of life) she was transferred to CPAP. From 34 4/7 weeks of PCA (66th day of life), the infant was transferred to supple-

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mental oxygen therapy through a loose-fitting face mask. Oxygenation was satisfactory; no signs of increased respiratory failure were diagnosed. On the 89th day of life (37 4/7 weeks of PCA), she was transferred to an oxygen tent (FiO_2 parameters were 0.3). She remained oxygen dependent throughout the entire observation period in the hospital.

At the age of 3 months, due to the appearance of repeated regurgitation, an X-ray contrast examination was performed, gastroesophageal reflux disease and hiatal hernia were detected. Consulted with a surgeon; surgical treatment is not indicated. At 3 months 1 week, the administration of an anti-regurgitation formula was started.

According to echocardiography performed at 38 5/7 weeks of PCA, the mean pulmonary artery pressure is equal to the systemic arterial pressure, there are a moderate right ventricular dilatation without significant myocardial hypertrophy and an atypical patent ductus arteriosus. In agreement with the pediatric cardiologist, therapy with sildenafil was started at a dose of 1.0 mg/kg 4 times a day.

According to the results of echocardiography (43 5/7 weeks of PCA), no signs of congenital heart disease were found, patent ductus arteriosus was not registered, moderate right heart dilation without significant myocardial hypertrophy maintained, the mean pulmonary artery pressure was 40–41 mmHg.

On Neurosonography (43 5/7 weeks of PCA) were diagnosed echo signs of post-hypoxic changes against the background of pronounced morpho-functional immaturity with asymmetric ventriculodilation, mainly due to the occipital horn of the large ventricle of the brain. There are periventricular leukomalacia (cystic form) and grade I intraventricular hemorrhage on the left side in anamnesis.

Electroencephalography data (43 6/7 weeks of PCA) indicated the presence of moderate diffuse changes in the functional state of neurons in the cortex and subcortical structures of the brain; There wasn't epileptiform activity or interhemispheric asymmetry.

Weight gain during observation in the hospital was: for the 1st and 2nd months — 785 g, for the 3rd month — 392 g, for the 4th month — 861 g.

Main diagnosis: Perinatal hypoxic-ischemic cerebral injury, periventricular leukomalacia (cystic form), early recovery period, pyramid deficiency syndrome in the lower extremities. Convulsive syndrome in anamnesis. Delayed psychomotor development.

Associated diagnosis: Bronchopulmonary dysplasia originating in the perinatal period, a "new" form, severe course, period of chronic disease, type I respiratory failure. Respiratory distress syndrome in anamnesis. Pulmonary hypertension. Prematurity 25 1/7 weeks. Extremely low birth weight. Proliferative retinopathy of prematurity, stage III, zone 2. Condition after undergoing laser coagulation of the left retina from 13.06.2017, of both eyes from 27.06.2017. Necrotizing enterocolitis in the fetus and newborn, stage 2a in anamnesis. Cytomegaloviral disease, unspecified. Generalized cytomegalovirus infection, viral carriage in anamnesis. Patent ductus arteriosus, medically closed. Anemia of prematurity, severe, of mixed origin. Acute hemorrhagic gastritis in anamnesis. Gastroesophageal reflux disease without esophagitis.

At 40 1/7 weeks of PCA, cardiorespiratory monitoring was performed during sleep while receiving supplemental oxygen therapy. Oxygen support was turned off for 92 minutes during monitoring to provide a true picture of the ability to maintain oxygen saturation within the target range. The recording duration was 258 minutes. The median oxygen saturation was 91,1% (the entire recording was analyzed), the minimum was 74,0% (recorded only in the absence of supplemental oxygen support). A total of 90 episodes of desaturation were recorded (oxygen desaturation index was 21,1 events/hour), of which 46 episodes (10,8 events/hour) were recorded with a drop in oxygen saturation <5%, 30 episodes were recorded with a drop in SpO_2 by 5–9% (7,0 events/hour), with a drop in SpO_2 by 10–20% — 13 episodes (3,0 events/hour) and with a drop in SpO_2 >20% — 1 episode (0,2 events/hour). All episodes of desaturation were observed in the absence of supplemental oxygen therapy. The number of episodes of desaturation <90% was 64 (15,0 events/hour), <85% — 37 episodes (8,7 events/hour), <80% — 12 episodes (2,8 events/hour). Severe bradycardia (83 beats per minute) was noted in the absence in the supplemental oxygen support. Based on the data obtained, it was decided to continue supplemental oxygen therapy at home.

At 48 3/7 weeks of PCA, repeated cardiorespiratory sleep monitoring was performed at home. Before the study, the infant had been without supplemental oxygen support for 7 days. The recording duration was 296 minutes. The median oxygen saturation during the infant's sleep (93,1 per cent) was lower than recommended standards. Positive dynamics were observed in the form of an

increase in median oxygen saturation compared to previous monitoring. The minimum value of median SpO_2 was 84,0%. Episodes of desaturation with independent recovery were diagnosed (oxygen desaturation index was 19,3 events/hour), with a drop in oxygen saturation <5% — 60 episodes (13,9 events/hour), 5–9% — 23 episodes (5,3 events/hour), 10–20% — 0 episodes. The number of episodes of decreased saturation <90% — 41 (9,5 events/hour), <85% — 1 episode (0,2 events/hour), <80% not registered. At the moments of desaturation, bradycardia was noted (96 beats per minute). Dynamic monitoring was recommended.

CONCLUSION

The formation of BPD in this infant was facilitated by factors such as mother's unfavorable obstetric and somatic anamnesis, premature birth, the need for intensive oxygen therapy due to type I respiratory failure, oxygen dependence up to five months of life. Characteristic clinical and radiological changes indicated the development of BPD. The need for supplemental oxygen therapy at 36 weeks of PCA suggests severe BPD. Hypoxic–ischemic brain injury, grade I intraventricular hemorrhage, and cystic periventricular leukomalacia were diagnosed. Cardiorespiratory sleep monitoring allowed us to establish positive dynamics in the form of an increase in the level of median oxygen saturation in the absence of oxygen support. However, attention is drawn to pronounced desaturation, accompanied by bradycardia, which requires dynamic monitoring.

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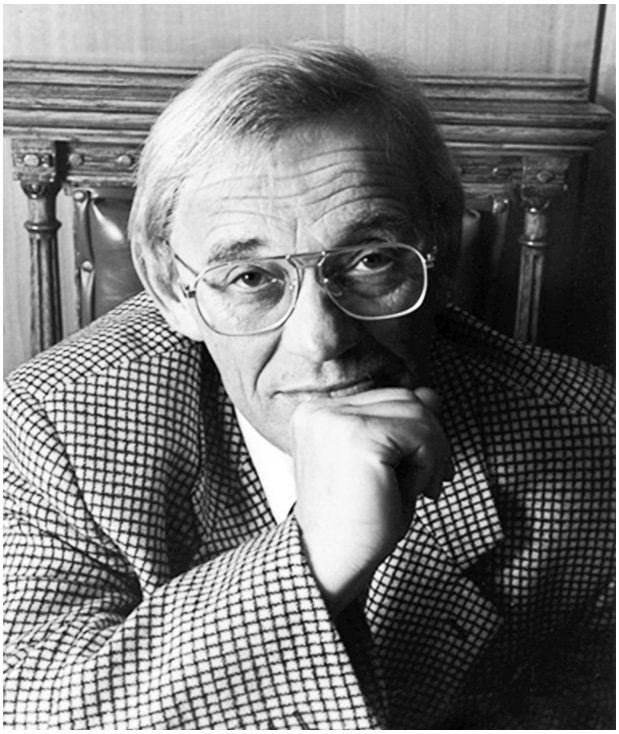
IN MEMORY OF A TEACHER. ABOUT NIKOLAI PAVLOVICH SHABALOV

ПАМЯТИ УЧИТЕЛЯ. О НИКОЛАЕ ПАВЛОВИЧЕ ШАБАЛОВЕ



Николай Павлович Шабалов
(21.03.1939–27.02.2023)

Nikolai Pavlovich was born on March 21, 1939 in Leningrad. When he was 2 years old, the Great Patriotic War began. He and his mother spent all 900 days of the blockade in their hometown. During the siege at the Leningrad Pediatric Medical Institute (LPMI), he was saved from severe pneumonia.

In 1956 N.P. Shabalov entered the LPMI. His teacher and mentor was an academician, head of the department of hospital pediatrics Alexander Fedorovich Tur. After graduating from the institute in 1962, Nikolai Pavlovich was admitted to this department, first as a clinical resident, and two years later as a postgraduate student. Under the guidance of A.F. Tur and professor of the Department of Biochemistry of LPMI A.A. Yuryev in 1967, Nikolai Pavlovich defended his PhD thesis on the topic "Adenosine triphosphatase activity of erythrocytes in acute leukemia in children."

"Blood of healthy children of different ages" (1970) is the first monograph co-authored with Teacher. In 1977, Nikolai Pavlovich defended his doctoral thesis "Pathogenesis, clinical picture, differential diagnosis and treatment of idiopathic thrombocytopenic purpura in children."

Not only hematology, but also neonatology developing at that moment attracted N.P. Shabalov. Understanding the relevance of the problem of nursing newborns, Nikolai Pavlovich took an active part in organizing and opening departments of pathology of newborns in the structure of the Children's City Hospital № 1 built in Leningrad. For remote monitoring of the condition of children in maternity hospitals, together with E.K. Tsybulkin, E.V. Guber, V.A. Lyubimenko developed the automated program "DINAR". In 1980, the first Reanimation and Consultation Center in the Soviet Union was opened, which is still operating today.

Since the opening of the hospital in 1977 and until 2016, N.P. Shabalov weekly advised the departments of resuscitation and pathology of newborns of Children's City Hospital № 1.

In 1985 N.P. Shabalov organized and headed the first department of pediatrics in Russia with courses in perinatology on the faculty of advanced training of doctors at the LPMI, the main task of which was the training and retraining of neonatologists. During the existence of the department, employees, postgraduate students, and applicants published 10 monographs, 14 textbooks, 3 guides for doctors, 4 reference books, 2 collections of scientific works and more than 300 different articles.

Since 1993, Nikolai Pavlovich headed the department and clinic of childhood diseases at the Military Medical Academy named after S.M. Kirov. Until 2009, Nikolai Pavlovich was the head of both departments. Since 2007, he became president of the St. Petersburg branch of the Union of Pediatricians of Russia.

Special credit goes to N.P. Shabalov in the organization of pediatric education in Russia. After numerous reissues of his textbooks, manuals and teaching aids both on general pediatrics and on individual sections of private pediatrics, it can be argued that the very concept of pediatric education today is being formed on the basis of these textbooks. The entire training program for pedia-

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tricians is essentially built on the basis of educational literature written by N.P. Shabalov.

N.P. Shabalov is the author and co-author of a large number of articles, monographs and manuals on perinatology. In this regard, it is worth noting his pioneering work on clinical pharmacology in neonates, perinatal hematology and hemostasiology, neonatal asphyxia, including asphyxia due to chronic intrauterine hypoxia, algorithms for primary newborn care in the maternity ward. N.P. Shabalov systematized the doctrine of borderline states of newborns and highlighted a number of new transitional states. He formulated the concept of the phase nature of changes in hemostasis, developed a classification of neonatal jaundice, and expressed a number of key considerations about perinatal infections and posthypoxic encephalopathy. The contribution of N.P. Shabalov to pediatric hematology is great. With the assistance of academician A.F. Tur, he turned out to be the author of the first in the Soviet Union age-related standards for peripheral blood parameters in children in the aspect of the physiology of hematopoiesis in various periods of childhood. In collaboration with A.V. Papayan, Nikolai Pavlovich was the author of the doctrine of hemorrhagic diathesis in infants. He first proved the role of hereditary thrombocytopathies in the pathogenesis of idiopathic thrombocytopenic purpura.

Nikolai Pavlovich is one of the few whose scientific work is based on a solid historical basis. Many of his studies are entirely devoted to the history of pediatrics.

Continuing the work begun by Academician A.F. Tur, N.P. Shabalov is the main initiator and inspirer of a new direction in pediatrics — perinatology, not only in theoretical terms, but also in its practical implementation. In collaboration with E.K. Tsybulkin and V.A. Lyubimenko, he created a coherent system of providing medical care for newborns in the metropolis, implemented throughout Russia.

It is difficult to list all the titles of the scientist — academician of the International Academy of Sciences of Ecology, Human Safety and Nature, honorary professor of the Kazakh National Medical University named after S.D. Asfendiyarov, honorary professor of the Children's Scientific and Clinical Center for Infectious Diseases, president of the regional branch of the Union of Pediatricians of Russia in St. Petersburg, Honored Scientist of the Russian Federation, laureate of the State Prize of the Russian Federation, Honored Doctor of the Russian Federation. Nikolai Pavlovich was awarded the Order of Honor (Russia), the Order of St. Michael the Archangel, numerous medals and other awards.

Nikolai Pavlovich's students are now working in all parts of Russia and the world. Under his leadership, 77 candidate and 24 doctoral dissertations were defended; Nikolai Pavlovich's students head departments in St. Petersburg, Chita, Nalchik, Irkutsk, Samarkand, and Bishkek.

Nikolai Pavlovich was an amazingly bright person who rejoiced at the success of his students more than his own. For the pediatricians of the country, he was like a universal Teacher. His memory will forever stay in our hearts.

Editor-in-Chief
"Children's medicine of the North-West",
Professor D.O. Ivanov
Главный редактор журнала
«Children's medicine of the North-West»,
профессор Д.О. Иванов

ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 15.03.2021 г.

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «Children's medicine of the North-West (Детская медицина Северо-Запада)» (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), Пи № ФС77–805334 от 1 марта 2021 г., именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

Автор передает Редакции для издания авторский оригинал или рукопись. Указанный авторский оригинал должен соответствовать требованиям, указанным в разделах «Представление рукописи в журнал», «Оформление рукописи». При рассмотрении полученных авторских материалов Журнал руководствуется «Едиными требованиями к рукописям, представляемым в биомедицинские журналы» (Intern. committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals // Ann. Intern. Med. 1997; 126: 36–47).

В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

Журнал не рассматривает работы, результаты которых по большей части уже были опубликованы или описаны в статьях, представленных или принятых для публикации в другие печатные или электронные средства массовой информации. Представляя статью, автор всегда должен ставить редакцию в известность обо всех направлениях этой статьи в печать и о предыдущих публикациях, которые могут рассматриваться как множественные или дублирующие публикации той же самой или очень близкой работы. Автор должен уведомить редакцию о том, содержит ли статья уже опубликованные материалы и предоставить ссылки на предыдущую, чтобы дать редакции возможность принять решение, как поступить в данной ситуации. Не принимаются к печати статьи, представляющие собой отдельные этапы незавершенных исследований, а также статьи с нарушением «Правил и норм гуманного обращения с биообъектами исследований».

Размещение публикаций возможно только после получения положительной рецензии.

Все статьи, в том числе статьи аспирантов и докторантов, публикуются бесплатно.

ПРЕДСТАВЛЕНИЕ РУКОПИСИ В ЖУРНАЛ

Авторский оригинал принимает редакция. Подписанная Автором рукопись должна быть отправлена в адрес редакции по электронной почте на адрес lt2007@inbox.ru. Автор должен отправить конечную версию рукописи и дать файлу название, состоящее из фамилии первого автора и первых 2–3 сокращенных слов из названия статьи. Информацию об оформлении можно уточнить на сайте: http://ojs3.gpmu.org/index.php/childmed/index.

СОПРОВОДИТЕЛЬНЫЕ ДОКУМЕНТЫ

К авторскому оригиналу необходимо приложить экспертное заключение о возможности опубликования в открытой печати (бланк можно скачать на сайте https://www.gpmu.org/science/pediatrics-magazine/).

Рукопись считается поступившей в Редакцию, если она представлена комплектно и оформлена в соответствии с описанными требованиями. Предварительное рассмотрение рукописи, не заказанной Редакцией, не является фактом заключения между сторонами издательского Договора.

Для публикации в Журнале необходимо предоставить рукопись и направление на публикацию от учреждения с разрешением на публикацию в открытой печати.

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.

АВТОРСКОЕ ПРАВО

Редакция отбирает, готовит к публикации и публикует переданные Авторами материалы. Авторское право на конкретную статью принадлежит авторам статьи. Авторский гонорар за публикации статей в Журнале не выплачивается. Автор передает, а Редакция принимает авторские материалы на следующих условиях:

1) Редакции передается право на оформление, издание, передачу Журнала с опубликованным материалом Автора для целей реферирования статей из него в Реферативном журнале ВИНИТИ, РНИЦ и базах данных, распространение Журнала/авторских материалов в печатных и электронных изданиях, включая размещение на выбранных либо созданных Редакцией сайтах в сети Интернет в целях доступа к публикации в интерактивном режиме любого заинтересованного лица из любого места и в любое время, а также на распространение Журнала с опубликованным материалом Автора по подписке;
2) территория, на которой разрешается использовать авторский материал, — Российская Федерация и сеть Интернет;
3) срок действия Договора — 5 лет. По истечении указанного срока Редакция оставляет за собой, а Автор подтверждает бессрочное право Редакции на продолжение размещения авторского материала в сети Интернет;
4) Редакция вправе по своему усмотрению без каких-либо согласований с Автором заключать договоры и соглашения с третьими лицами, направленные на дополнительные меры по защите авторских и издательских прав;
5) Автор гарантирует, что использование Редакцией предоставленного им по настоящему Договору авторского материала не нарушит прав третьих лиц;
6) Автор оставляет за собой право использовать предоставленный по настоящему Договору авторский материал самостоятельно, передавать права на него по договору третьим лицам, если это не противоречит настоящему Договору;
7) Редакция предоставляет Автору возможность безвозмездного получения справки с электронными адресами его официальной публикации в сети Интернет;
8) при перепечатке статьи или ее части ссылка на первую публикацию в Журнале обязательна.

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, место работы, почтовый адрес места работы, e-mail, ORCID. 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** (Summary) (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 аннотации: введение (Background), цели и задачи (Purposes and tasks), 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 целе-

сообразно 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** (Key words) от 3 до 10 ключевых слов или словосочетаний, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «ключевые слова». 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 точкой с запятой.

5. **Заголовки таблиц, подписи к рисункам**, а также все тексты на рисунках и в таблицах должны быть на русском и английском языках.

6. **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. 2005;10(2):49–53. ***Список формируется в порядке упоминания источников*** (если источник упоминается несколько раз, то используется номер ссылки первого упоминания). В описании указываются ВСЕ авторы публикации. Библиографические ссылки в тексте статьи даются цифрой в квадратных скобках. Ссылки на неопубликованные работы не допускаются.

Книга: Автор(ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания.

Если в качестве автора книги выступает редактор, то после фамилии следует ред.

Преображенский Б. С., Тёмкин Я. С., Лихачёв А. Г. Болезни уха, горла и носа. М.: Медицина; 1968.

Радзинский В. Е., ред. Перинеология: учебное пособие. М.: РУДН; 2008.

Brandenburg J. H., Ponti G. S., Worring A. F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY: Mosby; 1998.

Глава из книги: Автор (ы) название главы (знак точка) В кн.: или In: далее описание книги [Автор (ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания] (двоеточие) стр. от и до.

Коробков Г. А. Темп речи. В кн.: Современные проблемы физиологии и патологии речи: сб. тр. Т. 23. М.; 1989: 107–11.

Статья из журнала

Автор (ы) название статьи (знак точка) название журнала (знак точка) год издания (знак точка с запятой) том (если есть в круглых скобках номер журнала) затем знак (двоеточие) страницы от и до.

Кирющенков А. П., Совчи М. Г., Иванова П. С. Поликистозные яичники. Акушерство и гинекология. 1994; N 1: 11–4.

Brandenburg J. H., Ponti G. S., Worring A. F. Vocal cord injection with autogenous fat: a long-term magnetic resona. Laryngoscope. 1996; l06 (2, pt l): 174–80.

Тезисы докладов, материалы научных конф.

Бабий А. И., Левашов М. М. Новый алгоритм нахождения кульминации экспериментального нистагма (миниметрия). III съезд оториноларингологов Респ. Беларусь: тез. докл. Минск; 1992: 68–70.

Салов И. А., Маринушкин Д. Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». М.; 2000; ч. 1: 516–9.

Авторефераты

Петров С. М. Время реакции и слуховая адаптация в норме и при периферических поражениях слуха. Автореф. дис… канд. мед. наук. СПб.; 1993.

Описание Интернет-ресурса

Щеглов И. Насколько велика роль микрофлоры в биологии вида-хозяина? Живые системы: научный электронный журнал. Доступен по: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (дата обращения 02.07.2012).

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).

Для всех статей, имеющих DOI, индекс необходимо указывать в конце библиографического описания.

По новым правилам, учитывающим требования международных систем цитирования, библиографические списки (References) входят в англоязычный блок статьи и, соответственно,

должны даваться не только на языке оригинала, но и в латинице (романским алфавитом). Поэтому авторы статей должны давать список литературы в двух вариантах: один на языке оригинала (русскоязычные источники кириллицей, англоязычные латиницей), как было принято ранее, и отдельным блоком тот же список литературы (References) в романском алфавите для Scopus и других международных баз данных, повторяя в нем все источники литературы, независимо от того, имеются ли среди них иностранные. Если в списке есть ссылки на иностранные публикации, они полностью повторяются в списке, готовящемся в романском алфавите.

В романском алфавите для русскоязычных источников требуется следующая структура библиографической ссылки: автор(ы) (транслитерация), перевод названия книги или статьи на английский язык, название источника (транслитерация), выходные данные в цифровом формате, указание на язык статьи в скобках (in Russian).

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика.

На сайте http://www.translit.ru можно бесплатно воспользоваться программой транслитерации русского текста в латиницу. Программа очень простая.

1. Входим в программу Translit.ru. В окошке «варианты» выбираем систему транслитерации BGN (Board of Geographic Names). Вставляем в специальное поле весь текст библиографии на русском языке и нажимаем кнопку «в транслит».

2. Копируем транслитерированный текст в готовящийся список References.

3. Переводим с помощью автоматического переводчика название книги, статьи, постановления и т.д. на английский язык, переносим его в готовящийся список. Перевод, безусловно, требует редактирования, поэтому данную часть необходимо готовить человеку, понимающему английский язык.

4. Объединяем описания в соответствии с принятыми правилами и редактируем список.

5. В конце ссылки в круглых скобках указывается (in Russian). Ссылка готова.

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи

Книга: Avtor (y) Nazvanie knigi (znak tochka) [The title of the book in english] (znak tochka) Mesto izdaniya (dvoetochie) Nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya.

Preobrazhenskiy B. S., Temkin Ya. S., Likhachev A. G. Bolezni ukha, gorla i nosa. [Diseases of the ear, nose and throat]. M.: Meditsina; 1968. (in Russian).

Radzinskiy V. E., ed. Perioneologiya: uchebnoe posobie. [Perineology tutorial]. M.: RUDN; 2008. (in Russian).

Глава из книги: Avtor (y) Nazvanie glavy (znak tochka) [The title of the article in english] (znak tochka) In: Avtor (y) Nazvanie knigi (znak tochka) Mesto izdaniya (dvoetochie) Nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya]. (dvoetochie) stranisi ot i do.

Korobkov G. A. Temp rechi. [Rate of speech]. In.: Sovremennye problemy fiziologii i patologii rechi: sb. tr. T. 23. M.; 1989: 107–11. (in Russian).

Статья из журнала: Avtor (y) Nazvanie stat'I (znak tochka) [The title of the article in english] (znak tochka) Nazvanie zhurnala (znak tochka) god izdaniya (znak tochka s zapyatoy) tom (esli est' v kruglykh skobkakh nomer zhurnala) zatem (znak dvoetochie) stranitsy ot i do.

Kiryushchenkov A. P., Sovchi M. G., Ivanova P. S. Polikistoznye yaichniki. [Polycystic ovary]. Akusherstvo i ginekologiya. 1994; N 1: 11–4. (in Russian).

Тезисы докладов, материалы научных конф.

Babiy A. I., Levashov M. M. Novyy algoritm nakhozhdeniya kul'minatsii eksperimental'nogo nistagma (minimetriya). [New algorithm of finding of the culmination experimental nystagmus (minimetriya)]. III s'ezd otorinolaringologov Resp. Belarus': tez. dokl. Minsk; 1992: 68–70. (in Russian).

Salov I. A., Marinushkin D. N. Akusherskaya taktika pri vnutriutrobnoy gibeli ploda. [Obstetric tactics in intrauterine fetal death]. In: Materialy IV Rossiyskogo foruma «Mat' i ditya». M.; 2000; ch.1:516–9. (in Russian).

Авторефераты

Petrov S. M. Vremya reaktsii i slukhovaya adaptatsiya v norme i pri perifericheskikh porazheniyakh slukha. [Time of reaction and acoustical adaptation in norm and at peripheral defeats of hearing]. PhD thesis. SPb.; 1993. (in Russian).

Описание Интернет-ресурса

Shcheglov I. Naskol'ko velika rol' mikroflory v biologii vida-khozyaina? [How great is the microflora role in type-owner biology?]. Zhivye sistemy: nauchnyy elektronnyy zhurnal. Available at: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (accessed 02.07.2012). (in Russian).

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

Остальные материалы предоставляются либо на русском, либо на английском языке, либо на обоих языках по желанию.

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

Введение, изложение основного материала, заключение, литература. Для оригинальных исследований — введение, методика, результаты исследования, обсуждение результатов, литература (IMRAD).

В разделе «методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

Объем рукописей

Объем рукописи обзора не должен превышать 25 стр. машинописного текста через два интервала, 12 кеглем (включая таблицы, список литературы, подписи к рисункам и резюме на английском языке), поля не менее 25 мм. Нумеруйте страницы последовательно, начиная с титульной. Объем рукописи статьи экспериментального характера не должен превышать 15 стр. машинописного текста; кратких сообщений (писем в редакцию) — 7 стр.; отчетов о конференциях — 3 стр.; рецензий на книги — 3 стр. Используйте колонтитул — сокращенный заголовок и нумерацию страниц, для помещения вверху или внизу всех страниц статьи.

Иллюстрации и таблицы

Число рисунков рекомендуется не более 5. В подписях под рисунками должны быть сделаны объяснения значений всех кривых, букв, цифр и прочих условных обозначений. Все графы в таблицах должны иметь заголовки. Повторять одни и те же данные в тексте, на рисунках и в таблицах не следует. **Все надписи на рисунках и в таблицахприводятся на русском и английском языках.** Рисунки, схемы, фотографии должны быть представлены в точечных форматах tif, bmp (300–600 dpi), или в векторных форматах pdf, ai, eps, cdr. При оформлении графических материалов учитывайте размеры печатного поля Журнала (ширина иллюстрации в одну колонку — 90 мм, в 2 — 180 мм). Масштаб 1:1.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

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АДРЕС РЕДАКЦИИ

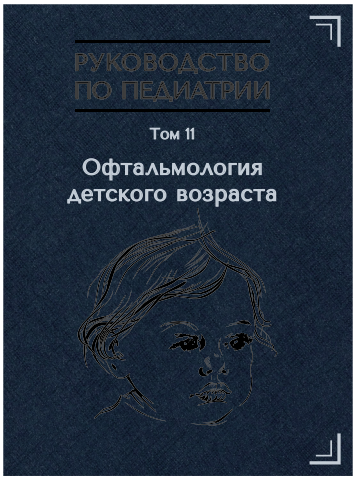
194100, Санкт-Петербург, Литовская ул., 2
e-mail: lt2007@inbox.ru.

Сайт журнала: http://ojs3.gpmu.org/index.php/childmed/index.

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.

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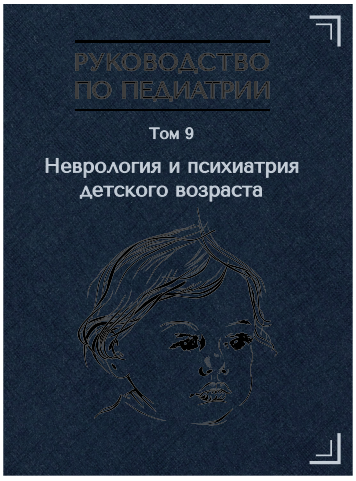
Редакционная коллегия тома: Д.О. Иванов, В.И. Гузева, С.В. Гречаный



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.

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