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ON THE ISSUE OF MEDICAL REHABILITATION: CURRENT LEVEL AND DEVELOPMENT PROSPECTS

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Abstract. The concern for the health of the population as the highest value in the Russian Federation dictates the necessity to seek the most advanced measures for patients of various ages to prevent disability and reduce the number of severe functional impairments that form during and as a result of illness, leading to limitations in physical and psychological aspects, as well as in the social aspect, including the educational process for children and the employment of adult patients, significantly reducing the level and quality of life. The global medical-social problem lies in providing comprehensive assistance to such categories of patients, which falls within the competence of medical rehabilitation. Its main tasks include maximizing the improvement of the functional state of patients to achieve the most complete recovery or compensation for the functions affected by the pathological process and enabling the fullest return to the usual social environment, including domestic, educational, and professional settings. Medical rehabilitation today is a relevant, modern, and successfully developing direction of domestic medicine, based on the scientific and practical knowledge and skills of such confidently established medical disciplines included in the rehabilitation process as therapeutic physical culture and sports medicine, physiotherapy, reflexology, and manual therapy. Physicians specializing in these disciplines, under the guidance and coordination of a physician specializing in medical rehabilitation or physical and rehabilitation medicine, together with a narrow-profile specialist and, if necessary, involving specialists in clinical psychology, corrective pedagogy, social workers, and others, form interdisciplinary teams aimed at providing maximally early, individual, comprehensive, systematic, and prolonged in time necessary assistance to the children and adult population of our country at all stages of medical rehabilitation. Thanks to effective and individual rehabilitation programs, it is possible to more successfully solve such serious tasks as reducing the level of disability, the percentage of people with disabilities, reducing the duration of incapacity for work, and improving the quality and level of life, which ultimately meets the most important objectives of domestic healthcare: preserving and strengthening the health of the citizens of the Russian Federation and preventing adverse outcomes of diseases.

Key words: *medical rehabilitation; rehabilitation potential; rehabilitation diagnosis; rehabilitation prognosis; stages of medical rehabilitation.*

К ВОПРОСУ О МЕДИЦИНСКОЙ РЕАБИЛИТАЦИИ: СОВРЕМЕННЫЙ УРОВЕНЬ И ПЕРСПЕКТИВЫ РАЗВИТИЯ

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Резюме. Забота о здоровье населения как наивысшей ценности в Российской Федерации диктует необходимость поиска наиболее совершенных мероприятий для пациентов различного возраста по профилактике инвалидизации и снижению числа тяжелых функциональных нарушений, формирующихся в течение и результате болезни, приводящих к появлению ограничений возможностей, как в физическом и психологическом плане, так и в социальном аспекте, включая образовательный процесс у детей и трудовую деятельность у взрослых пациентов, что значимо снижает уровень и качество жизни. Глобальная медико-социальная проблема заключается во всесторонней помощи таким категориям пациентов, что входит в компетенции медицинской реабилитации, основными задачами которой является максимальное улучшение функционального состояния больных с целью наиболее полного восстановления или компенсации пострадавших в результате патологического процесса функций, а также наиболее полноценное возвращение в привычную социальную, в том числе бытовую, образовательную и профессиональную среду. Медицинская реабилитация сегодня — актуальное современное и успешно развивающееся направление отечественной медицины, которое базируется на научно-практических знаниях и умениях таких уверенно зарекомендовавших себя медицинских дисциплин, входящих в состав реабилитации, как лечебная физическая культура и спортивная медицина, физиотерапия, рефлексотерапия, мануальная терапия. Врачи данных специальностей под руководством и координацией врача по медицинской реабилитации или врача по физической и реабилитационной медицине, совместно с узким профильным специалистом, а при необходимости — с подключением специалистов по клинической психологии, коррекционной педагогике, социальных работников и других, входят в состав междисциплинарных бригад, призванных оказывать максимально раннюю, индивидуальную, комплексную, систематичную и пролонгированную во времени необходимую помощь детскому и взрослому населению нашей страны на всех этапах медицинской реабилитации. Благодаря эффективным и индивидуальным программам медицинской реабилитации возможно более успешное решение таких серьезных задач, как снижение уровня инвалидизации, процента людей с ограниченными возможностями здоровья, сокращение сроков нетрудоспособности, повышение качества и уровня жизни, что в конечном итоге будет отвечать важнейшим задачам отечественного здравоохранения: сохранение, укрепление здоровья граждан Российской Федерации и профилактика неблагоприятных исходов заболеваний.

Ключевые слова: *медицинская реабилитация; реабилитационный потенциал; реабилитационный диагноз; реабилитационный прогноз; этапы медицинской реабилитации.*

Under the definition of "rehabilitation", *rehabilis* (from the Latin *re* — renewal, *habilitas* — ability, suitability), according to the translation from Latin, means the restoration of abilities, suitability for anything or properties, which reflects the presence of both biological and social components of this concept [1–4].

The World Health Organization interprets the concept of rehabilitation as follows: "Rehabilitation is a set of activities — medical rehabilitation, psychological rehabilitation, pedagogical rehabilitation, social rehabilitation and legal rehabilitation, designed to provide persons with disabilities with maximum adaptability to living conditions in society" [1, 2].

Medical rehabilitation is a relatively young area in medicine, which appeared during the First World War and has actively developed since the second half of the 20th century. Initially, medical rehabilitation was considered an integral part of the treatment process, but now medical rehabilitation should be considered as a central component of a comprehensive rehabilitation process [1, 5].

"Rehabilitation 2030: a call to action" is the global strategic plan adopted by the World Health Organization in 2017 [3, 6].

The functional responsibilities of a medical rehabilitation specialist (also a *physical medicine* and *rehabilitation physician*) are presented in the Order of the Ministry of Labor of the Russian Federation dated 03.09.2018 № 572n *"On approval of the professional standard "Medical rehabilitation* specialist" [7, 8].

Orders of the Ministry of Health of the Russian Federation dated 31.07.2020 № 788n "On approval of the procedure for organizing medical rehabilitation for adults" and dated 23.10.2019 № 878n "On approval of the procedure for organizing medical rehabilitation for children" are regulatory documents governing the organization of medical rehabilitation for the child population in the Russian Federation, according to which medical rehabilitation is carried out in the following conditions: outpatient, day hospital or inpatient, depending on the child's condition and the ability to achieve the set rehabilitation goals [9, 10].

According to the Order of the Ministry of Health of the Russian Federation dated 02.05.2023 № 206n "On approval of qualification requirements for medical and pharmaceutical workers with higher education," the following specialties were introduced: instructor-methogist in physical therapy (non-medical education); medical psychologist, clinical psychologist (non-medical education); physical rehabilitation specialist (kinesiologist, non-medical education) [11].

In practice, a variety of therapeutic methods of medical rehabilitation are widely used, including therapeutic and surgical strategies, as well as alternative non-drug technologies and innovations [1, 3, 12–14].

The most advanced technologies have been developed with the participation of microprocessor information devices for managing digital "cloud" data; they represent, in particular, biocontroled and robotic medical equipment [3].

The patterns of influence on the human body of numerous means of rehabilitation, primary physical factors and exercises, the action of which is justified from a scientific and practical point of view, are at the origins of medical rehabilitation and are called upon to normalize sanogenesis [3, 15–19].

The staged nature and differentiated approach of rehabilitation programs in case of reversible functional impairments should ensure the restoration of the health of the population and its maintenance at a decent level. In the formation of irreversible morphological changes in the body, the focus should shift to achieving and maintaining compensation for impaired functions. In addition, it is important to carry out secondary prevention of the occurrence of diseases and relapses, the development of possible complications [1].

Rehabilitation should be considered as a process of recovery, a return to the original state of physical, personal and social status in pathological conditions diagnosed in patients at different ages, after early childhood. On the contrary, habilitation involves a set of measures carried out in the case of congenital or early acquired disorders with the aim of forming and further developing physical, personal and social indicators. The methods used in habilitation differ from rehabilitation methods — these are pedagogical and psychological developmental methods [2, 20].

In the absence of significant restrictions, a treatment strategy that affects the etiopathogenesis of the disease is indicated; combining the efforts of therapeutic and rehabilitation tactics is determined by the presence of disability or the risk of its formation. A fundamentally new section — physical and rehabilitation medicine — is designed to study the influence of physical methods on the body of physical methods and means available in the arsenal of medical rehabilitation to solve the problems of patients with persistent limitations [3].

Rehabilitation is understood as the restoration of health, functions and performance of people affected by diseases, injuries, exposed to factors of various nature: physical, chemical and social [2].

The result of rehabilitation is the achievement of the maximum possible physical, mental, professional, social fullness and economic self-sufficiency in the case of a specific disease, which is possible with the provision of necessary and timely medical and social assistance [1].

Rehabilitation today is a serious pressing problem of national healthcare, which has a diverse vector focus and includes, along with the compulsory medical component, the participation to a greater or lesser extent of the psychological, labor, social and economic spheres [1, 21, 22].

The most important goals of rehabilitation include a recovery of psychological status, normalization of personal characteristics, as well as the earliest and fullest possible return of patients to work and everyday skills, their successful integration into society [2, 23–25].

According to the goals set, the most important tasks of rehabilitation are put forward, which include the full recovery of the functional state of various organs and systems of the body, and, if necessary, the formation of compensatory adaptations to the conditions of daily life; normalization of household skills; carrying out secondary prevention measures in the direction of preventing the occurrence of deviations from the norm in people's health [2].

The leading principles of medical rehabilitation include the following positions: according to indications, the earliest possible start, an integrated approach, the validity of rehabilitation measures, the development of an individual rehabilitation program, compliance with stages,, continuity and succession during the rehabilitation process, the work of a multidisciplinary team, prolongation in time until confident positive dynamics, availability of rehabilitation measures [2].

The social orientation of rehabilitation programs is important, the compulsory use in the

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practice of monitoring the adequacy of the loads administered to patients and assessing the effectiveness of the rehabilitation methods used [1].

The need for medical rehabilitation is justified in cases of real possibility of eliminating or reducing the consequences of the disease. Depending on the severity of functional disorders, the body responds with one of the options: restitution, regeneration or compensation [3].

Thus, medical rehabilitation should not be considered as a direction for further treatment of patients in whom high effects cannot be expected. Only the earliest possible inclusion in the treatment process, starting from resuscitation, of necessary and possible rehabilitation techniques will contribute to the best outcome of the disease, as well as secondary prevention of disability [1, 2].

It is important to note that there are no general contraindications for rehabilitation measures; there are only contraindications for specific methods. Carrying out postural correction in a very serious patient's condition is indicated and is the beginning of the rehabilitation process [1].

The basic principles of medical rehabilitation are: the provisions of the International Classification of Functioning, the selection of the most effective minimum of rehabilitation measures, compliance with the necessary performance criteria at each stage of medical rehabilitation, the formation of an information infrastructure among rehabilitation institutions, the availability of a unified routing management system for specialized patients [2, 26].

Of particular note is the International Classification of Functioning, Disability and Health, proclaimed by the World Health Organization in 2002, which, thanks to validated categories of health and associated characteristics, helps to establish a rehabilitation profile, monitor and objectively assess the effectiveness of rehabilitation measures [3, 27–29].

According to modern scientific ideas, the following areas of rehabilitation are distinguished, systematized by E.I. Aukhadeyev [2]:

- noorehabilitation — recovery of the patient's intellectual capabilities;
- psychorehabilitation — normalization of the components of the patient's mental health, in particular emotional, volitional and other areas;
- sensory rehabilitation — recovery of both the senses and the ability to perceive a variety of sensations;
- logo rehabilitation — recovery of pronunciation speech and related internal functions of the language;
- kinesitherapy — recovery of motor function at different levels of complexity in various pathologies;
- vegetative rehabilitation — normalization of the functional state of internal organs, recovery of vegetative processes;
- ergo rehabilitation — recovery of vital processes, labor activity;
- eco-rehabilitation — recovery of adaptive abilities to both the natural and social environment;
- ludorehabilitation — involves stimulating the creative capabilities of the individual;
- self-rehabilitation — normalization of the personal characteristics of a particular individual.

When providing medical rehabilitation assistance, the stability of the patient's clinical condition is essential, regardless of the duration of the disease; at the same time, the risk of possible complications should not exceed the rehabilitation potential; there should also be no contraindications to the prescription of certain methods, taking into account the rehabilitation diagnosis [1].

The definition of rehabilitation potential is the key point to the successful implementation of rehabilitation measures.

For this purpose, both clinical manifestations and functional disorders, characteristic features of somatic and psychological status are subject to careful study, which are the necessary foundation for the recovery of affected functions and serve as a decisive moment for the prospects for recovery or the ability to compensate for the limitations that have arisen.

Rehabilitation potential is usually understood as an objective perspective of the patient's functional recovery over the expected period of rehabilitation care, taking into account the clinical picture of the disease in a particular patient, the availability of individual resources and compensatory capabilities, provided that the psychosomatic state is stable against the background of high motivation for the rehabilitation program [1].

Thus, rehabilitation potential is a set of biological and psychological characteristics of the patient, as well as social and environmental aspects that determine the possible extent of realization of his potential.

There are high, medium and low levels of rehabilitation potential. In particular, high rehabilitation potential is characterized by a disease duration of no more than three months in the absence of information about a progressive pathological process, occurs in children, young or middle-aged people with good motivation of the patient or child's parents for rehabilitation, in older people with preserved cognitive status and, as a rule, an adequate psycho-emotional background or its minor changes [1].

Only high rehabilitation potential implies full recovery or a high level of functional recovery of the body as a result of the selected rehabilitation protocol.

A moderately expressed level of rehabilitation potential is characterized by a disease duration of no more than a year in the absence of information about a progressive pathological process; in this case, patients under the supervision with moderate changes in weight and height parameters, with adequate cognitive status and, as a rule, moderate deviations in the psycho-emotional background, amenable to slight pharmacological correction [1].

In patients with a disease duration of more than 1–2 years, a progressive course, significant deviations in weight and height parameters (in middle-aged and older people), pronounced disorders of a healthy lifestyle — alcoholism or drug addiction (in middle-aged and older people), severe cognitive and emotional disorders that require serious correction, as a rule, reveal a low level of rehabilitation potential.

In the case of moderate rehabilitation potential, only partial, and with low rehabilitation potential, insignificant, even non-existent, recovery of impaired body functions as a result of the rehabilitation process is possible [1].

To solve rehabilitation problems, indicators of physical development and physical endurance are determined, the degree of development and stability of the psycho-emotional sphere, the level of social adaptation, including the ability to acquire familiar household and work skills and abilities are identified [23–25].

A rehabilitation diagnosis is understood as a diagnosis that reflects an assessment of the emerging functional consequences of the disease. It consists of a description of the injury and subsequent impairments, both household and professional, indicating restrictions on activity and participation in private life and society, with an emphasis on environmental factors that can relieve or aggravate the patient's basic life functions [1].

It is necessary to carefully examine the patient in order to establish his rehabilitation diagnosis for the subsequent formation of an individual rehabilitation program. This examination consists of collecting anamnestic data, complaints, as well as the necessary set of laboratory and instrumental studies with the obligatory determination of the influence of physical disorders on the functional state of the body, the degree of preservation of everyday and professional skills [1].

A multidisciplinary approach is central to medical rehabilitation, with the participation and close cooperation of medical, psychological, pedagogical, social and professional specialists to provide all necessary types of assistance and correct the resulting consequences of the disease, for a gradual return to a normal lifestyle, with the maximum functional recovery or compensation of the impaired functions in the absence of the proper level of rehabilitation potential [1, 2, 18].

An individually formed multidisciplinary team consists of: a physical medicine and rehabilitation physician, a profile specialist (attending physician), a doctor in physical therapy and sports medicine, a physiotherapist, a medical psychologist; if necessary, a reflexology therapist, a chiropractor; nurses, both specialized in medical rehabilitation and care; according to indications — specialists in laboratory and instrumental diagnostics, adaptive physical culture, as well as in correctional pedagogy (speech therapy, deaf pedagogy, typhlopedagogy, oligophrenopedagogy), clinical psychology, including neuropsychologists, specialists in social work, vocational guidance and occupational therapy, who have undergone advanced training in methods rehabilitation of patients of the corresponding profile [1, 2, 18].

The tasks of the multidisciplinary team include the development of an individual rehabilitation program for a particular patient, followed by the implementation of a set of rehabilitation measures and mandatory monitoring of the adequacy of the loads and their effectiveness [1].

Specialists of a multidisciplinary team provide assistance to patients as a single whole, and it is very important for each of them to clearly know their functional responsibilities and close cooperation of all specialists with each other [1, 2, 18].

Options for the work of a multidisciplinary team may include joint patient visits, medical commissions and consultations, explanatory con-

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versations with relatives and care staff. Multidisciplinary team specialists assess the level of rehabilitation potential, outline rehabilitation goals and a rehabilitation plan, in which the patient and relatives can participate, and establish contact with outpatient polyclinic service for further assistance [2].

A multidisciplinary team determines the most likely prospect for the development of compensatory and adaptive capabilities in each clinical case.

During the rehabilitation process, an analysis of the functional response of various organs and systems to the presented diverse load is carried out. Strict dosing of physical activity and an adequate choice of means of therapeutic and rehabilitation training are important: preference should be given fractional loads of a gradual plan, the necessary ratio of activity and rest, and mandatory consideration of the individual characteristics of the patient [30].

The effectiveness of the individual rehabilitation measures, as well as the medical rehabilitation program in general, is assessed objectively over time for timely correction strategies, if necessary.

Thus, the result of rehabilitation largely depends on the coordinated professional participation of each member of the multidisciplinary team at all stages of medical rehabilitation. However, the nature and intensity of the work of specialists differs as the pathological process develops in the patient [1, 2, 18].

The rehabilitation goal is the real planned result of the rehabilitation program, which is determined at a meeting of the multidisciplinary team with the possible participation of the patient himself.

The goal of rehabilitation will be in direct correlation with the degree of initial anatomical, functional disorders and social deviations: in some cases it is possible to achieve complete recovery of the affected functions with a full return to the social environment, in others we will only be talking about possible compensation of impaired functions for maximum adaptation in household and professional spheres, improving the level and quality of life [1, 2, 18].

Carrying out medical rehabilitation is justified within three stages, which depends on the severity of the existing violations.

In the resuscitation department and intensive care unit of medical institutions, assistance is provided at the first stage of medical rehabilitation to patients in the acute period of illness, if there is sufficient rehabilitation potential and there are no contraindications to the planned methods of rehabilitation measures. Medical rehabilitation assistance at this stage is carried out according to the profile of the identified pathology in accordance with existing clinical protocols.

Inpatient departments of rehabilitation and rehabilitation centers provide assistance within the second stage of medical rehabilitation for patients in the early recovery period of the disease, late rehabilitation period, in the period of residual symptoms and in the chronic course of the disease outside the exacerbation during current hospitalization. These patients must also be objectively confirmed to have the rehabilitation potential necessary to solve the planned rehabilitation tasks [1].

Outpatient care, as well home care by mobile teams, is considered the third stage of medical rehabilitation for patients in early or late residual periods, as well as during the period of residual symptoms of the disease and in the chronic course of the pathological process outside the exacerbation. In this case, to obtain an effective result of rehabilitation measures, a sufficient level of rehabilitation potential is also necessary. In the departments and offices of rehabilitation, physiotherapy, physical therapy, reflexology, manual therapy, psychotherapy, medical psychology, speech therapist (teacher of the deaf, typhlopedagogue and other specialists in the field) the necessary amount of qualified, including high-tech assistance is provided with the inclusion of modern strategies and innovations in the field medical rehabilitation.

In especially severe cases, when patients, due to their functional capabilities, cannot do without outside help, without the necessary level of rehabilitation potential to significantly improve their condition, medical care is provided in care organizations and consists of maintaining the achieved or existing functional state with the maximum possible adaptation environment to the level of individual functionality [1].

The successful result of rehabilitation measures is characterized by stabilization of the physical, psychological and social aspects of the health and life of patients, and their fullest integration into the usual society [2].

However, for certain medical indications, patients can continue the rehabilitation process in the sanatorium-resort conditions, depending

on the profile of the existing pathology [31, 32]. In this case, resort therapeutic factors in combination with the recommended regimen, including diet therapy, the indicated intensity of physical activity, contribute to the improvement of the psychophysical state, and in the most curable cases, the normalization of previously existing activities, including recovery in the professional sphere, which has a positive effect on the overall emotional the mood for recovery or the maximum possible compensation of affected functions, improving the quality of life [1, 2, 18].

Sanatorium-resort treatment has a preventive focus, which will be true both for preventing the further development of a newly occurring disease, occurs for the first time, and strengthening the body, and for anti-relapse purposes, as well as for reducing the degree of progression of a previously diagnosed pathological process [2, 15–17, 33].

Thus, medical rehabilitation is currently facing serious and pressing challenges due to the increasing number of people with chronic diseases and disabilities among patients of different ages.

All modern technologies, strategies and innovations included in the complex of rehabilitation measures are currently aimed at recovering and maximizing compensation for the impaired functions of the rehabilitator.

Based on the principles of medical rehabilitation, multidisciplinary team specialists, professionally trained within the scope of their competencies, under the guidance of a rehabilitation medicine doctor or a physical medicine and rehabilitation physician, form individual rehabilitation programs with mandatory monitoring of their effectiveness and safety.

Vector orientations of rehabilitation to normalize the physical, psychological, social, educational and professional aspects, together with motivating trainings for patients and their relatives about the necessity and importance of the rehabilitation process, will contribute to the achievement of the most satisfactory recovery results and an optimistic post-rehabilitation prognosis for the life and health of the people of our country.

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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REFERENCES

1. Korolev A.A., Sobolevskaya Yu.A., Rudakova S.M. i dr. Meditsinskaya reabilitatsiya. [Medical rehabilitation]. Uchebnoye posobiye. Pod red. S.S. Aleksanina. Vseros. tsentr ekstren. i radiats. meditsiny im. A.M. Nikiforova MCHS Rossii. Sankt-Peterburg; 2014. (In Russian).
2. Meditsinskaya reabilitatsiya. [Medical rehabilitation]. Uchebnik. Pod red. V.A. Yepifanova, A.N. Razumova, A.V. Yepifanova. 3-ye izd., pererab. i dop. Moskva; 2023. (In Russian).
3. Ponomarenko G.N. Vosstanovitel'naya meditsina: fundamental'nyye osnovy i perspektivy razvitiya. [Regenerative medicine: fundamental principles and development prospects]. Fizicheskaya i reabilitatsionnaya meditsina. 2022; 4(1): 8–20. (In Russian).
4. Fizicheskaya i reabilitatsionnaya meditsina. [Physical and rehabilitation medicine]. Natsional'noye rukovodstvo. Pod red. G.N. Ponomarenko. Moskva; 2016. (In Russian).
5. Nechayev V.S., Magomedova Z.A. Meditsinskaya reabilitatsiya: istoriya voprosa i definitsii. [Medical rehabilitation: history of the issue and definitions]. Problemy sotsial'noy gigiyeny, zdravookhraneniya i istorii meditsiny. 2017; 25(4): 221–5. DOI: 10.18821/0869-866X-2017-25-4221-225. (In Russian).
6. Ponomarenko G.N. Vosstanovitel'naya meditsina: fundamental'nyye osnovy i perspektivy razvitiya. [Regenerative medicine: fundamental principles and development prospects]. Fizicheskaya i rea-

bilitatsionnaya meditsina. 2022; 4(1): 8–20. DOI: 10.26211/2658-4522-2022-4-1-8-20. (In Russian).
7. Prikaz Ministerstva truda i sotsial'noy zashchity RF ot 03.09.2018 №572n «Ob utverzhdenii professional'nogo standarta «Spetsialist po meditsinskoy reabilitatsii». [On approval of the professional standard "Medical Rehabilitation Specialist"]. [Elektronnyy resurs]. URL: http://publication.pravo.gov.ru/Document/View/0001201809200018. (In Russian).
8. Martsiyash A.A., Kolmykova Ye.V., Baturina N.P. i dr. Fizicheskaya i reabilitatsionnaya meditsina — novaya spetsial'nost' v nomenklature spetsial'nostey. Istoriya, tseli, zadachi. [Physical and rehabilitation medicine is a new specialty in the range of specialties. History, goals, objectives]. Meditsina v Kuzbasse. 2020; 19(2): 28–33. DOI: 10.24411/2687-0053-2020-10014. (In Russian).
9. Prikaz Ministerstva zdravookhraneniya Rossiyskoy Federatsii ot 23.10.2019 №878n «Ob utverzhdenii poryadka organizatsii meditsinskoy reabilitatsii detey». [On approval of the procedure for organizing medical rehabilitation of children]. [Elektronnyy resurs]. URL: http://publication.pravo.gov.ru/Document/View/0001201912240050. (In Russian).
10. Prikaz Ministerstva zdravookhraneniya Rossiyskoy Federatsii ot 31.07.2020 № 788n «Ob utverzhdenii poryadka organizatsii meditsinskoy reabilitatsii vzroslym». [On approval of the procedure for organizing medical rehabilitation for adults]. [Elektronnyy resurs]. URL: http://publication.pravo.gov.ru/Document/View/0001202009250036. (In Russian).
11. Prikaz Ministerstva zdravookhraneniya Rossiyskoy Federatsii ot 02.05.2023 № 206n «Ob utverzhdenii kvalifikatsionnykh trebovaniy k meditsinskim i farmatsevticheskim rabotnikam s vysshim obrazovaniyem». [On approval of qualification requirements for medical and pharmaceutical workers with higher education]. [Elektronnyy resurs]. URL: http://publication.pravo.gov.ru/document/0001202306010041. (In Russian).
12. Yepifanov V.A., Yushchuk N.D., Yepifanov A.V. Mediko-sotsial'naya reabilitatsiya posle infektsionnykh zabolevaniy. [Medical and social rehabilitation after infectious diseases]. Moskva; 2020. (In Russian).
13. Yepifanov V.A., Korchazhkina N.B. Meditsinskaya reabilitatsiya pri zabolevaniyakh i povrezhdeniyakh organov mochevydeleniya. [Medical rehabilitation for diseases and injuries of the urinary organs]. Moskva; 2019. (In Russian).
14. Meditsinskaya reabilitatsiya: fiziologicheskiye i molekulyarno-geneticheskiye osnovy effektivnosti. [Medical rehabilitation: physiological and molecular genetic basis of effectiveness]. Pod red. d-ra med. nauk prof. S.G. Shcherbaka. SPb GBUZ «Gorodskaya bol'nitsa № 40». Sankt-Peterburg; 2022. (In Russian).
15. Fizioterpiya i kurortologiya. [Physiotherapy and balneology]. Pod red. V.M. Bogolyubova. Kniga I. Moskva; 2020. (In Russian).
16. Fizioterpiya i kurortologiya. [Physiotherapy and balneology]. Pod red. V.M. Bogolyubova. Kniga II. Moskva; 2020. (In Russian).
17. Fizioterpiya i kurortologiya. [Physiotherapy and balneology]. Pod red. V.M. Bogolyubova. Kniga III. Moskva; 2020. (In Russian).
18. Khan M.A., Razumov A.N., Pogonchenkova I.V. i dr. Fizicheskaya i reabilitatsionnaya meditsina v pediatrii. [Physical and rehabilitation medicine in pediatrics]. 2-ye izd., pererab. i dop. Moskva; 2022. (In Russian).
19. Khan M.A., Krivtsova L.A., Demchenko V.I. Fizioterapiya v pediatrii. [Physiotherapy in pediatrics]. Moskva; 2014. (In Russian).
20. Puzin S.N., Memetov S.S., Shurgaya M.A. i dr. Aspekty reabilitatsii i abilitatsii invalidov na sovremennom etape. [Aspects of rehabilitation and habilitation of disabled people at the present stage]. Mediko-sotsial'naya ekspertiza i reabilitatsiya. 2016; 19(1): 4–7. DOI: 10.18821/1560-9537-2016-19-1-4-7. (In Russian).
21. Meditsinskaya reabilitatsiya. [Medical rehabilitation]. Pod red. A.V. Yepifanova, Ye.Ye. Achkasova, V.A. Yepifanova. Moskva; 2015. (In Russian).
22. Ivanova G.Ye. Meditsinskaya reabilitatsiya v Rossii. Perspektivy razvitiya. Consilium Medicum. [Medical rehabilitation in Russia. Development prospects]. Consilium Medicum. 2016; 18(2.1): 9–13. (In Russian).
23. Bulekbayeva A.S., Kusainova K.K., Zhakenova A.S., Khamadiyeva A.F. Ergoterapiya kak odno iz napravleniy v reabilitatsii detey s ogranichennymi vozmozhnostyami. [Occupational therapy as one of the areas in the rehabilitation of children with disabilities]. Vestnik AGIUV. 2014; 1: 19–23. (In Russian).
24. Mal'tseva M.N., Shmonin A.A., Mel'nikova Ye.V., Ivanova G.Ye. Ergoterapiya. Rol' vosstanovleniya aktivnosti i uchastiya v reabilitatsii patsiyentov. [Occupational therapy. The role of activity restoration and participation in patient rehabilitation]. Consilium Medicum. 2017; 19(2.1.): 90–3. (In Russian).
25. Malysheva S.N., Lobach-Khomutova M.P. Primeneniye elementov ergoterapii dlya razvitiya detey s ogranichennymi vozmozhnostyami. [Application of elements of occupational therapy for the development of children with disabilities]. Innovatsionnaya nauka. 2020; 1: 149–51. (In Russian).

26. Aukhadeyev E.I. Mezhdunarodnaya klassifikatsiya funktsionirovaniya, ogranicheniy zhiznedeyatel'nosti i zdorov'ya, rekomendovannaya VOZ, — novyy etap v razvitii reabilitologii. [The International Classification of Functioning, Disability and Health, recommended by WHO, is a new stage in the development of rehabilitation science]. Kazan. med.zhurn. 2007; 88(1): 5–9. (In Russian).
27. Ponomarenko G.N. Mezhdunarodnaya klassifikatsiya funktsionirovaniya, ogranicheniy zhiznedeyatel'nosti i zdorov'ya — instrument nauchnoy otsenki effektivnosti meditsinskoy reabilitatsii. [The International Classification of Functioning, Disability and Health is a tool for scientific assessment of the effectiveness of medical rehabilitation]. Voprosy kurortologii, fizioterapii i lechebnoy fizicheskoy kul'tury. 2013; 90(2): 57–62. (In Russian).
28. Ponomarenko G.N., Shoshmin A.V., Besstrashnova Ya.K., Cherkashina I.V. Primeneniye Mezhdunarodnoy klassifikatsii funktsionirovaniya, ogranicheniy zhiznedeyatel'nosti i zdorov'ya dlya otsenki effektivnosti reabilitatsii: metodologiya, praktika, rezul'taty. [Application of the International Classification of Functioning, Disability and Health to assess the effectiveness of rehabilitation: methodology, practice, results]. Voprosy kurortologii, fizioterapii i lechebnoy fizicheskoy kul'tury. 2016; 93(6): 12–20. (In Russian).
29. Ponomarenko G.N., Shoshmin A.V., Besstrashnova Ya.K., Cherkashina I.V. Planirovaniye i otsenka effektivnosti reabilitatsii bol'nykh osteoartrozom: ispol'zovaniye bazovogo nabora Mezhdunarodnoy klassifikatsii funktsionirovaniya, ogranicheniy zhiznedeyatel'nosti i zdorov'ya. [Planning and evaluating the effectiveness of rehabilitation of patients with osteoarthritis: using the core set of the International Classification of Functioning, Disability and Health]. Voprosy kurortologii, fizioterapii i lechebnoy fizicheskoy kul'tury. 2017; 94(1): 4–9. (In Russian).
30. Fizicheskaya reabilitatsiya. [Physical rehabilitation]. V 2 t. T.1: ucheb. dlya stud. uchrezhdeniy vyssh. med. prof. obrazovaniya. Pod red. S.N. Popova. Moskva; 2013. (In Russian).
31. Razumov A.N., Ponomarenko G.N., Zhuravlev A.I., Sokurov A.V. i dr. Sanatorno-kurortnoye lecheniye invalidov v Rossiyskoy Federatsii. [Sanatorium-resort treatment of disabled people in the Russian Federation]. Voprosy kurortologii, fizioterapii i lechebnoy fizicheskoy kul'tury. 2021; 98(6): 5–15. DOI: 10.17116/kurort2021980615. (In Russian).
32. Vladimirova O.N., Afonina K.P., Ponomarenko G.N., Shoshmin A.V. Organizatsiya sistemy kompleksnoy reabilitatsii v Rossiyskoy Federatsii na osnove izucheniya potrebnostey invalidov. [Organization of a system of comprehensive rehabilitation in the Russian Federation based on studying the needs of people with disabilities]. Meditsina v Kuzbasse. 2018; 17(4): 20–7. (In Russian).
33. Kotenko K.V., Korchazhkina N.B., Khan M.A. Osnovnyye napravleniya razvitiya detskoy kurortologii i sanatorno-kurortnogo lecheniya detey v Rossiyskoy Federatsii. [The main directions of development of children's balneology and sanatorium-resort treatment of children in the Russian Federation]. Kremlevskaya meditsina. Klinicheskiy vestnik. 2016; 3: 7–11. (In Russian).

ЛИТЕРАТУРА

1. Королев А.А., Соболевская Ю.А., Рудакова С.М. и др. Медицинская реабилитация. Учебное пособие. Под ред. С.С. Алексанина. Всерос. центр экстрен. и радиац. медицины им. А.М. Никифорова МЧС России. СПб.; 2014.
2. Медицинская реабилитация. Учебник. Под ред. В.А. Епифанова, А.Н. Разумова, А.В. Епифанова. 3-е изд., перераб. и доп. М.; 2023.
3. Пономаренко Г.Н. Восстановительная медицина: фундаментальные основы и перспективы развития. Физическая и реабилитационная медицина. 2022; 4(1): 8–20.
4. Физическая и реабилитационная медицина. Национальное руководство. Под ред. Г.Н. Пономаренко. М.; 2016.
5. Нечаев В.С., Магомедова З.А. Медицинская реабилитация: история вопроса и дефиниции. Проблемы социальной гигиены, здравоохранения и истории медицины. 2017; 25(4): 221–5. DOI: 10.18821/0869-866X-2017-25-4221-225.
6. Пономаренко Г.Н. Восстановительная медицина: фундаментальные основы и перспективы развития. Физическая и реабилитационная медицина. 2022; 4(1): 8–20. DOI: 10.26211/2658-4522-2022-4-1-8-20.
7. Приказ Министерства труда и социальной защиты РФ от 03.09.2018 № 572н «Об утверждении профессионального стандарта «Специалист по медицинской реабилитации». [Электронный ресурс]. URL: http://publication.pravo.gov.ru/Document/View/0001201809200018.
8. Марцияш А.А., Колмыкова Е.В., Батурина Н.П. и др. Физическая и реабилитационная медицина — новая специальность в номенклатуре специальностей. История, цели, задачи. Медицина в Кузбассе. 2020; 19(2): 28–33. DOI: 10.24411/2687-0053-2020-10014.
9. Приказ Министерства здравоохранения Российской Федерации от 23.10.2019 № 878н «Об ут-

верждении порядка организации медицинской реабилитации детей». [Электронный ресурс]. URL: http://publication.pravo.gov.ru/Document/View/0001201912240050.
10. Приказ Министерства здравоохранения Российской Федерации от 31.07.2020 № 788н «Об утверждении порядка организации медицинской реабилитации взрослым». [Электронный ресурс]. URL: http://publication.pravo.gov.ru/Document/View/0001202009250036.
11. Приказ Министерства здравоохранения Российской Федерации от 02.05.2023 №206н «Об утверждении квалификационных требований к медицинским и фармацевтическим работникам с высшим образованием». [Электронный ресурс]. URL: http://publication.pravo.gov.ru/document/0001202306010041.
12. Епифанов В.А., Ющук Н.Д., Епифанов А.В. Медико-социальная реабилитация после инфекционных заболеваний. М.; 2020.
13. Епифанов В.А., Корчажкина Н.Б. Медицинская реабилитация при заболеваниях и повреждениях органов мочевыделения. М.; 2019.
14. Медицинская реабилитация: физиологические и молекулярно-генетические основы эффективности. Под ред. д-ра мед. наук проф. С.Г. Щербака. СПб ГБУЗ «Городская больница № 40». СПб.; 2022.
15. Физиотерпия и курортология. Под ред. В.М. Боголюбова. Книга I. М.; 2020.
16. Физиотерпия и курортология. Под ред. В.М. Боголюбова. Книга II. М.; 2020.
17. Физиотерпия и курортология. Под ред. В.М. Боголюбова. Книга III. М.; 2020.
18. Хан М.А., Разумов А.Н., Погонченкова И.В. и др. Физическая и реабилитационная медицина в педиатрии. 2-е изд., перераб. и доп. М.; 2022.
19. Хан М.А., Кривцова Л.А., Демченко В.И. Физиотерапия в педиатрии. М.; 2014.
20. Пузин С.Н., Меметов С.С., Шургая М.А. и др. Аспекты реабилитации и абилитации инвалидов на современном этапе. Медико-социальная экспертиза и реабилитация. 2016; 19(1): 4–7. DOI: 10.18821/1560-9537-2016-19-1-4-7.
21. Медицинская реабилитация. Под ред. А.В. Епифанова, Е.Е. Ачкасова, В.А. Епифанова. М.; 2015.
22. Иванова Г.Е. Медицинская реабилитация в России. Перспективы развития. Consilium Medicum. 2016; 18(2.1): 9–13.
23. Булекбаева А.С., Кусаинова К.К., Жакенова А.С., Хамадиева А.Ф. Эрготерапия как одно из направлений в реабилитации детей с ограниченными возможностями. Вестник АГИУВ. 2014; 1: 19–23.
24. Мальцева М.Н., Шмонин А.А., Мельникова Е.В., Иванова Г.Е. Эрготерапия. Роль восстановления активности и участия в реабилитации пациентов. Consilium Medicum. 2017; 19(2.1.): 90–3.
25. Малышева С.Н., Лобач-Хомутова М.П. Применение элементов эрготерапии для развития детей с ограниченными возможностями. Инновационная наука. 2020; 1: 149–51.
26. Аухадеев Э.И. Международная классификация функционирования, ограничений жизнедеятельности и здоровья, рекомендованная ВОЗ, — новый этап в развитии реабилитологии. Казан. мед. журн. 2007; 88(1): 5–9.
27. Пономаренко Г.Н. Международная классификация функционирования, ограничений жизнедеятельности и здоровья — инструмент научной оценки эффективности медицинской реабилитации. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2013; 90(2): 57–62.
28. Пономаренко Г.Н., Шошмин А.В., Бесстрашнова Я.К., Черкашина И.В. Применение Международной классификации функционирования, ограничений жизнедеятельности и здоровья для оценки эффективности реабилитации: методология, практика, результаты. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2016; 93(6): 12–20.
29. Пономаренко Г.Н., Шошмин А.В., Бесстрашнова Я.К., Черкашина И.В. Планирование и оценка эффективности реабилитации больных остеоартрозом: использование базового набора Международной классификации функционирования, ограничений жизнедеятельности и здоровья. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2017; 94(1): 4–9.
30. Физическая реабилитация. В 2 т. Т. 1: учеб. для студ. учреждений высш. мед. проф. образования. Под ред. С.Н. Попова. М.; 2013.
31. Разумов А.Н., Пономаренко Г.Н., Журавлев А.И., Сокуров А.В. и др. Санаторно-курортное лечение инвалидов в Российской Федерации. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2021; 98(6): 5–15. DOI: 10.17116/kurort2021980615.
32. Владимирова О.Н., Афонина К.П., Пономаренко Г.Н., Шошмин А.В. Организация системы комплексной реабилитации в Российской Федерации на основе изучения потребностей инвалидов. Медицина в Кузбассе. 2018; 17(4): 20–7.
33. Котенко К.В., Корчажкина Н.Б., Хан М.А. Основные направления развития детской курортологии и санаторно-курортного лечения детей в Российской Федерации. Кремлевская медицина. Клинический вестник. 2016; 3: 7–11.

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KETOGENIC DIET IS A NON-DRUG METHOD OF TREATING EPILEPSY

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Abstract. The article presents data on the possibilities of using a ketogenic diet in patients with epilepsy. The relevance of the topic is due to the fact that drug treatment of this disease leads to seizure relief in less than 70% of cases, and therefore there is a need to use alternative therapies. Experimental and clinical data on the results of treatment with the ketogenic diet were analyzed, and the mechanisms underlying its clinical effects were considered.

Key words: *epilepsy; ketogenic diet; ketone bodies; neurotransmitters; paroxysms; microbiota.*

КЕТОГЕННАЯ ДИЕТА — НЕМЕДИКАМЕНТОЗНЫЙ СПОСОБ ЛЕЧЕНИЯ ЭПИЛЕПСИИ

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Резюме. В статье представлены данные о возможностях применения кетогенной диеты у пациентов с эпилепсией. Актуальность темы обусловлена тем, что медикаментозное лечение данного недуга приводит к купированию приступов менее чем в 70% случаев, в связи с чем существует необходимость использования альтернативных методов терапии. Проанализированы экспериментальные и клинические данные о результатах применения кетогенной диеты, а также рассмотрены механизмы, лежащие в основе ее клинических эффектов.

Ключевые слова: *эпилепсия; кетогенная диета; кетоновые тела; нейромедиаторы; пароксизмы; микробиота.*

INTRODUCTION

Epilepsy is a chronic, polyetiological disease of the brain, characterized by repeated unprovoked (or reflex) seizures of disturbances in motor, autonomic, sensory and mental functions resulting from *excessive* electrical *neuronal discharges*. This definition was given by the main regulatory body of the actions of epileptologists - the International League Against Epilepsy (ILAE), created more than 100 years ago. The presented formulation of the disease remains relevant today, although with minor additions [1, 2]. The onset of the disease is observed mainly in childhood (about 75% of all cases) [3]. The mechanisms of development of paroxysms are quite complex, and the etiological factors are multifaceted. Although still in 40–60% of patients, the cause of epilepsy remains unknown [1, 4, 5].

The main clinical manifestations of epilepsy in children are epileptic seizures, occurring in the form of tonic-clonic seizures, absence seizures,

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myoclonus with loss of consciousness or with preserved consciousness. Often, epileptic paroxysms occur in an atypical, erased manner. Instrumental and laboratory diagnosis of this disease includes electroencephalogram (EEG), skull radiography, computed tomography (CT), magnetic resonance imaging (MRI) and brain positron emission tomography (PET), biochemical blood test and cerebrospinal fluid analysis.

Classic treatment of epilepsy in children involves the observance of the protective regime, taking anticonvulsants, psychotherapy, and, if necessary, neurosurgical intervention. Despite the therapy, in more than 30% of patients with epilepsy, seizures are not able to be reduced, but have a progressive nature, that is, so-called refractory epilepsy is noted [6]. Even the addition of alternative treatments, such as neurostimulation and surgery, does not always provide a positive effect.

It has been proven that uncontrolled epilepsy has a negative impact on the quality of life of both the patients themselves and their relatives and friends, and this this requires the development of new, more promising treatment areas.

KETOGENIC DIET AS AN ALTERNATIVE METHOD OF TREATING EPILEPSY

The relationship between the central nervous system (CNS) and the ketogenic diet (KD) has been known for over a century. The first KD was developed by Dr. Russell Morse Wilder in 1921 at the Mayo Clinic [7, 8].

KD can be successfully used to compensate for a group of severe neurological diseases [9, 10] and is recommended for children as an alternative treatment for any form of epilepsy when traditionally used antiepileptic drugs are ineffective (recommendation level A, evidence level 1) [11].

By definition, a traditional KD is a low-carbohydrate, high-fat, moderate-protein diet that aims to replace glucose with ketone bodies (KBs) [7–10, 12]. The so-called *VLCKD model* is very-low-carbohydrate KD.

For constant mental work, the brain needs glucose as the fastest and most reliable way to obtain energy. Once in the bloodstream, glucose crosses the blood-brain barrier (BBB) with the help of carrier proteins and provides neurons with fuel.

When glucose reserves in the hepatocyte mitochondria are depleted as a result of β-oxidation, KBs (acetoacetate, β-hydroxybutyrate (β-HB), acetone) are formed from fatty acids, which, thanks to special monocarboxylate transporters, enter the blood from the liver and then pass through the BBB and provide energy to brain cells. Although it is known that the brain cannot exist solely due to KBs [12–14].

Thus, during glucose deficiency, KBs (mainly β-hydroxybutyrate) become the energy substrate for the production of adenosine triphosphate (ATP), a universal energy molecule, in cells throughout the body, including the brain. This metabolic shift causes many neurobiochemical, neuroplastic and hormonal changes, resulting in a decrease in neuronal excitability and, accordingly, the frequency of seizures.

The positive therapeutic effect of KD for the reduce seizures is confirmed by many clinical studies.

First, for glucose transporter type 1 deficiency syndrome (GLUT-1 is the main transporter that removes glucose from the luminal membrane of the BBB capillaries), VLCKD is the main and only treatment method.

GLUT-1 deficiency syndrome is a genetic metabolic encephalopathy with various focal and multifocal types of seizures (classic epileptic variant, occurs in 90% of patients). Mutations in the SLC2A1 gene, encoding the GLUT-1 synthesis, disrupt glucose transport to the brain. Transferring a patient with this pathology to KD provides neurons with "fuel" due to the fact that CBs pass through the BBB using other transport proteins (MCT1).

The work of foreign and native-born scientists has proven that early initiation and lifelong adherence to VLCKD guarantees children with GLUT-1 deficiency syndrome, a normal level of psychomotor, speech, motor, cognitive development and the absence of epileptic paroxysms [15, 16].

Secondly, the results of two meta-analyses confirmed the positive therapeutic effect of KD in epilepsy.

The first, including 7 studies involving 427 children and adolescents with epilepsy, demonstrated a reliable decrease in seizure frequency by an average of 85% after 3 months of adherence to VLCKD [17].

The second meta-analysis, presenting the results of 12 studies (270 patients) of the use of various variants of KD in drug-resistant epilepsy, showed its overall effectiveness in 42% of patients [18]. Similar data were obtained from the analysis of single works of the period from 1946 to 2019: 13 studies involving 932 participants, of which 711 were children from 4 months to 18 years [19–22]. The authors noted that VLCKD is most effective in patients with generalized epilepsy [23].

Thirdly, the experience of Moscow neurologists, dietitians and nutritionists using VLCKD both

in combination with anticonvulsant therapy and other non-drug methods in the treatment of refractory epilepsy in children from 1 to 18 years of age indicates a reduction in the number of seizures by more than 50% in 50–85% of children. It has been noted that an integrated approach, involving a differentiated choice of one or another treatment method, can achieve significant positive results [24–26].

However, recent experimental work reveals that KD, which has been established since 1921, has a large number of side effects. Thus, scientists at the University of California in an in *vivo study* obtained data on the negative effect of such VLCKD on the cognitive abilities of mice under hypoxic conditions [27].

Currently, for the treatment of refractory epilepsy in both children and adults, it has been proposed to use a modified Atkins diet, in which the body obtains about 45% of its energy from substituted medium-chain fatty acid residues of triglycerides (MCTs), and not by the metabolism of long-chain fatty acids (LCFA), as in the classic version of KD. To maintain daily energy balance in the diet, the carbohydrate component of the diet is slightly increased, mainly due to sugars with a low glycemic index, as stable glucose levels are shown to be related to seizure control [28].

In addition to the Atkins ketogenic diet, it is possible to prescribe a modified Mediterranean-ketogenic diet (MMKD) with different ratios of fats, proteins and carbohydrates. MMKD includes olive oil as the main source of polyphenols and monounsaturated fatty acids (MUFAs), which have an antioxidant profile [29, 30].

Such "relatively" gentle diets are more accessible and more physiological for both brain activity and the intestines, despite the fact that discussions about their therapeutic effectiveness continue [31].

A large randomized controlled trial (RCT) conducted by V. Sondhi et al. (2020) with the participation of children (n=158), compared the effectiveness of classical KD, Atkins KD and MMKD in preventing seizures in patients. The researchers found that while all dietary interventions showed improvement compared to the control group, traditional KD was most effective in reducing episodes and severity of seizures [32].

These days, most ketogenic diets are customized, modified KDs that balance ketogenic effects with palatability.

As scientists study the practicality of modified KD, they are seeking to determine the molecular mechanisms of anticonvulsant action and identify whether the responsiveness of treatment depends on the length of the carbon skeleton [31].

MECHANISMS OF KETOGENIC DIET ACTION

The main pathogenetic action of KD, aimed at suppressing excitability in brain cells, has not been fully studied, but a number of hypotheses are being considered about the direct influence of ketones, which are [31, 33]:

- reduce ATP production from glucose oxidation and the opening of ATP-sensitive potassium channels, and also enhance GABA-mediated inhibition;
- change the mitochondrial permeability of mitochondrial membranes, reducing the severity of mitochondrial dysfunction, oxidative stress and cell death;
- inhibit adenosine kinases with a subsequent increase in adenosine levels and activation of adenosine A1 receptors.

In addition, a series of scientific studies have found that ketones affect the metabolism of amino acids in neurons, and, accordingly, the metabolism of neurotransmitters. It has been noted that when following a modified Atkins KD, the concentration of glutamate in brain tissue decreases and the level of γ-aminobutyric acid (GABA) increases [31, 34].

In vitro experiments with neuronal cell cultures assessing the effects of all amino acids demonstrated that CTs sharply reduce the concentrations of three amino acids: leucine, arginine and glutamine, resulting in inhibition of mTOR, a DEPDC5-dependent signaling pathway, and a decrease in the anticonvulsant activity of neuronal cells [21].

The intracellular signaling peptide mTOR is one of the universal signaling pathways characteristic of most human cells and is involved in many neurological disorders. Excessive induction of this molecule increases the susceptibility of neurons to seizures. *The signaling* by a *protein* called DEPDC5 acts as a brake on the mTOR pathway. Many people with epilepsy have mutations in the *DEPDC5* gene, which are associated with focal epilepsy, infantile spasms, and even sudden infant death syndrome [35].

Animal studies have shown that high concentrations of acetone and β-HB stimulate GABA and glycine receptors, and brain cell saturation with β-hydroxybutyrate is inversely related to seizure severity [36–38]. Accumulation of acetoacetate inhibits voltage-gated calcium channels in hippocampal pyramidal cells, thereby inhibiting neuronal excitability. In addition, ketones can compete with chlorine in the vesicular glutamate

transport, inhibiting glutamatergic transmission and, consequently, seizure activity [38].

Thus, the increased content of ketones and, above all, β-HB is the main anticonvulsant mechanism of KD in people with epilepsy, especially when it is not amenable to drug treatment [39].

It is believed that the energy profile of brain cells is influenced not only by ketones, but also by the fatty acids themselves. Once in brain cells, they undergo β-oxidation directly in astrocytes, thereby increasing the production of CBs directly in glial cells.

It has been noted that the shorter the chain length of fatty acids, the easier it penetrates into the mitochondrial matrix, where it binds to a high-energy bond with coenzyme A and provides the synthesis of CBs and ATP [31, 34].

The anticonvulsant effect of decanoic (capric — $CH_3(CH_2)_8COOH$) and octanoic (caprylic — $CH_3(CH_2)_6COOH$) fatty acids (FAs) is dynamically studied in animal models. The main food source of these FAs is coconut oil.

The anticonvulsant effect of decane FA is predetermined by its ability in micromolar concentrations to selectively block AMPA receptors (an ionotropic glutamate receptor that transmits fast excitatory signals at synapses of the nervous system) [38] and induce peroxisome proliferator activated receptor γ (PPARγ), which leads to increased mitochondrial function, increases the mitochondrial complex I activity and stimulates mitochondrial biogenesis in neurons [18, 34].

The anticonvulsant activity of octane FA is associated with a non-selective effect on adenosine receptors. Moreover, its derivatives (5-methyloctanoic acid) demonstrate AMPA-dependent control of seizures both *in vitro* and *in vivo* [31].

A number of experimental and clinical studies have found that polyunsaturated fatty acids (PUFAs) are also capable of providing anticonvulsant protection, especially docosahexaenoic acid (DHA, 22:6n-3), a derivative of α-linolenic PUFA (the omega-3 class) [40]. PUFAs can stimulate peroxisome proliferator-activated receptors (PPARs—a group of nuclear receptors that function as transcription factors), which regulate anti-inflammatory, antioxidant, and mitochondrial genes, leading to increased energy reserves, stabilization of synaptic function, and restriction of increased excitability [41].

DHA regulates neuronal activity through interaction with ion channels and release of neurotransmitters [42]. A study of children (case–control) revealed a lower omega-3/omega-6 ratio in the blood serum of patients with epilepsy compared to healthy [43]. *In vitro* and *in vivo* studies have shown that the DHA-rich diet is useful for controlling epilepsy, but clinical data have been somewhat inconsistent [40]. A meta-analysis of seven clinical studies conducted in 2021 confirmed that dietary omega-3 supplementation significantly reduced seizure frequency and was more effective in adults than in children [44].

In the last decade, the role of the intestinal microbiota in the antiepileptic effect of the ketogenic diet has been actively discussed [45, 46]. The presented hypothesis has several scientific and clinical explanations.

Firstly, no one doubts that food is the main factor determining the gut microbiome. Accordingly, the transformation of the diet in the form of adherence to the classical CD with very low content of carbohydrates (VLCKD), predominantly complex, makes significant changes in the α- and β-diversity of the gut microbiome, both at the level of bacterial types and at the level of species and genera of microorganisms and, therefore, it is involved in the treatment of epilepsy [33, 46].

A study conducted by G. Xie (2017) showed that children with epilepsy have an imbalance of gut microbiome before the onset of VLCKD. Adherence to the diet induces the growth of bacteria of the *Bacterioides* species and significantly reduces the number of pathogenic proteobacteria (*Escherichia, Salmonella* and *Vibrio*), which are in high titer in the basic analysis. The authors noted the association of *Bacteroides* spp. with the digestion and metabolism of high-fat nutrients and the regulation of IL-6 and IL-17 secretion by dendritic cells, due to the consequences of seizures in patients with epilepsy. Researchers have suggested that VLCKD may reduce these symptoms by promoting changes in microbiota diversity [47].

Secondly, the general transformation of the gut microbiome helps to improve the relationship between *Firmicutes* and *Bacteroides* species due to the relative increase in bacteria of the *Bacteroides* species, which have a more favorable effect on the host body and CNS as well. It is important to note the identified two-stage effect of VLCKD: at the beginning of the diet, there is a sharp decrease in bacterial richness and diversity, but after 12 weeks, the concentration of bacteria gradually returns to the baseline level, significantly exceeding it by the 23–24th week of strict adherence to the prescribed diet [48].

And third, gut microbiome secretes a range of chemicals: cytokines, neuroactive molecules (neu-

rotransmitters, neuropeptides), chemokines, endocrine messengers, and microbial metabolites such as short-chain fatty acids (SCFAs), branched-chain amino acids, and peptidoglycans that directly promote communication between the gut and the brain, influencing various neuroendocrine, neuroimmune and metabolic processes. For example, it has been noted that GABA, the main inhibitory neurotransmitter of CNS mammals, including humans, is produced by strains of *Lactobacilli* and *Bifidobacteria*, more precisely *Lactobacillus brevis, Bifidobacterium denteum, Bifidobacterium bifidum*. In hippocampal damage or status epilepticus, GABA synthesized by the microbiome can lead to an imbalance between the GABA and glutamate systems, causing seizures. The gut also produce 90% of serotonin thanks to microorganisms such as *Enterococcus* spp., *Streptococcus* spp. and *Escherichia* spp. [49]. Serotonin binding to 5-HT receptors in microglia in the white or gray matter of the brain activates the release of cytokine-carrying exosomes, providing a mechanism for gut-induced modulation of neuroinflammation [50]. Another microbial metabolite that influences the microglia activity is tryptophan, a serotonin precursor [51]. Bacterial metabolites derived from dietary tryptophan may control CNS inflammation through a mechanism mediated by aryl hydrocarbon receptors (Ahr), affecting microglial activation and the transcriptional program of astrocytes [51].

Various neurotransmitters produced by the microbiota can pass through the intestinal mucosa, but rarely through the BBB, with the exception of GABA. However, they have the potential to influence microbiota-gut-brain (MGB or BGM) signaling, regulating enteric vagal afferent activity and inflammatory reactions. Moreover, bidirectional transmission of biochemical signals takes place [52–55]. However, the exact mechanism behind these phenomena still needs to be studied.

Experimental studies examining the relationship of VLCKD with antiepileptic effects in mice noted significant changes in the structure of intestinal taxonomic units over 4 days of the diet. Two species of bacteria, Akkermansia and Parabacteroides, increased significantly in mice fed a ketogenic diet. Subsequent colonization of gnotobiotic mice by these microorganisms provided them with anticonvulsant protection, which was associated with a decrease in the subpopulation of ketogenic (leucine) and glutamylated (glutamine) (GG) amino acids both in the gut and in the bloodstream, as well as inhibition of the production of the microsomal enzyme — γ-glutamyl transpeptidase (GGTP) by the gut microbiome [56]. It is assumed that GG amino acids have transport properties through the BBB that are different from non-glutamylated forms. This feature of glutamylated amino acids increases the ratio of GABA to glutamate in the mouse brain. It has been suggested that VLCKD-associated limitation of microbiota and GG amino acids plays a key role in the antiepileptic effect.

It has been noted that KD causes diversification of the gut microbiota, namely a decrease in the number of pro-inflammatory microbes such as Desulfovibrio and Turicibacter, as well as an increase in the number of beneficial bacteria *Akkermansia muciniphila* and *Lactobacillus plantarum*, capable of produsing SCFAs that can modulate neurotransmitters such as glutamate, glutamine, GABA and neurotrophic factors [57].

Some SCFAs (propionate and butyrate) have an anticonvulsant effect because they provide maturation of brain microglia and reduce the permeability of the BBB. Butyrate improves mitochondrial dysfunction and protects brain tissue from oxidative stress and apoptosis through the Keap/Nrf2/HO-1 pathway, thereby increasing the seizure threshold and reducing seizure intensity [58]. In addition, propionate and butyrate influence the cellular signaling system by modifying intracellular potassium levels [59], which, in turn, regulate the expression levels of tryptophan 5-hydroxylase 1, involved in the synthesis of serotonin, and tyrosine hydroxylase. The latter enzyme is necessary in the biosynthesis of dopamine, adrenaline and norepinephrine [60]. It has been established that SCFAs are able to indirectly affect the MGB axis by inducing the release of several gastrointestinal hormones, such as glucagon-like peptide-1 (GLP-1) and leptin, through the enteroendocrine cells. These gastrointestinal hormones can interact with the vagus nerve and even brain receptors [61–64].

Despite the growing body of evidence, a number of questions still remain about the mechanisms by which KD may protect patients with epilepsy from seizures. For example, how does modulation of bacterial species influence changes in the membrane potential of hippocampal neurons? Is modulation of GABA/glutamate levels a major pathway? How might changes in bacterial species modulate GABA/glutamate levels [33]?

Therefore, specialized and restricted diets adopted for the treatment of certain diseases need to be studied for their effect on the human microbiota (for example, FODMAP control for irritable bowel syndrome and the ketogenic diet for re-

fractory epilepsy). These patterns, by reducing or eliminating a particular food type, can positively or negatively influence the composition of the microbiota and the associated effect on host physiology. This refers to the very-low-carbohydrate ketogenic diet (VLCKD), a nutritional approach that is gaining popularity not only for treating neurological disorders but also for rapid weight loss.

CONCLUSION

Currently, about 25–30% of patients diagnosed with epilepsy are refractory to treatment with antiepileptic drugs (AEDs). Uncontrolled seizures can lead to cognitive disorders, such as memory and learning impairment, as well as varying degrees of permanent brain dysfunction and even death. Side effects of AEDs may limit their use in some patients. Such people need improved alternative treatments, one of which is the ketogenic diet.

For people with refractory epilepsy who are unable to undergo neurosurgical intervention, the ketogenic diet remains the main and only method of therapy. However, further research is needed to confirm this position.

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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REFERENCES

1. Erofeev N.P., Radchenko V.G., Seliverstov P.V. Klinicheskaya fiziologiya tolstoy kishki. Mekhanizmy deystviya korotkotsepochechnykh zhirnykh kislot v norme i pri patologii. [Clinical physiology of the colon. Mechanisms of action of short-chain fatty acids in normal and pathological conditions]. Sankt-Peterburg; 2012. (In Russian).
2. Voronkova K.V. Epilepsii v praktike pediatra. [Epilepsy in the practice of a pediatrician]. Praktika pediatra. 2015; 1: 54–63. (In Russian).
3. Guzeva O.V., Guzeva V.I., Guzeva V.V. i dr. Rezul'taty otsenki kachestva lecheniya i zhizni detey s epilepsiey. [Results of evaluation of the quality of treatment and life of children with epilepsy]. Pediatr. 2017; 2. (In Russian).
4. Beghi E., Giussani G., Abd-Allah F.A. et al. Global, Regional, and National Burden of Epilepsy, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019; 18: 357–75.
5. Dahlin M., Prast-Nielsen S. The gut microbiome and epilepsy. EBioMedicine. 2019; 44: 741–6.
6. Kobow K., Blümcke I. Epigenetics in Epilepsy. Neurosci Lett. 2018; 667: 40–6.
7. Wheless J.W. History of the ketogenic diet Epilepsia. 2008; 49(8): 3–5.
8. Meira I. D'Andrea, Romão T.T., Pires do Prado H.J. et al. Ketogenic Diet and Epilepsy: What We Know So Far. Front. Neurosci. 2019; 13: 5.
9. Lobo F., Haase J., Brandhorst S. The Effects of Dietary Interventions on Brain Aging and Neurological Diseases. Nutrients. 2022; 14(23): 5086.
10. Dyńka D., Kowalcze K., Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases. Nutrients. 2022; 14(23): 5003.
11. Klinicheskie rekomendatsii. Epilepsiya i epileptycheskiy status u vzroslykh i detey. [Epilepsy and epileptic status in adults and children]. MZ RF. 2022. (In Russian).
12. Kossoff E.H., Zupec-Kania B.A., Auvin S. et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018; 3(2): 175–92.
13. Baranovskiy A.Yu. Dietologiya. [Dietetics]. Rukovodstvo. Sankt-Peterburg: Piter Publ.; 2012. (In Russian).
14. Pediatriya. [Pediatrics]. Nats. ruk-vo. Pod red. A.A. Baranova. Moskva: GEOTAR-Media Publ. 2009; 1. (in Russian)
15. Ramm-Pettersen A., Selmer K.K., Nakken K.O. Glucose transporter protein type 1 (GLUT-1) deficiency syndrome. Tidsskr Nor Laegeforen. 2011; 131(8): 828–31.
16. Luk'yanova E.G., Ayvazyan S.O., Osipova K.V. i dr. Opyt primeneniya ketogennoy diety u patsientov s sindromom defitsita transportera glyukozy 1 tipa (klinicheskoe nablyudenie). [Experience

with the ketogenic diet in patients with type 1 glucose transporter deficiency syndrome (clinical observation)]. Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova. 2015; 115(5-2): 53–60. (In Russian).
17. van der Louw E., van den Hurk D., Neal E. et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol. 2016; 20(6): 798–809.
18. Ye F., Li X.J., Jiang W.L. et al. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015; 11(1): 26–31.
19. Martin K., Jackson C.F., Levy R.G., Cooper P.N. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2016.
20. Neal E.G., Chaffe H., Schwartz R.H. et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008; 7(6): 500–6.
21. Lambrechts DAJE., de Kinderen RJA., Vles JSH. et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017; 135(2): 231–9.
22. Zare M., Okhovat A.A., Esmaillzadeh A. et al. Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial. Iran. J. Neurol. 2017; 16: 72–7.
23. Liu H., Yang Y., Wang Y. et al. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. Epilepsia Open. 2018; 3(1): 9–17.
24. Luk'yanova E.G., Fyvazyan S.O., Osipova K.V. et al. Kognitivnye i motornye funktsii u detey s farmakorezistentnymi formami epilepsii, nakhodyashchikhsya na ketogennoy diete. [Cognitive and motor functions in children with drug-resistant forms of epilepsy on a ketogenic diet]. Zh. Epilepsiya i paroksizmal'nye sostoyaniya. 2016; 8(1): 37–42. (In Russian).
25. Ayvazyan S.O., Shiryaev Yu.S. Sovremennye metody lecheniya patsientov s farmakorezistentnoy epilepsiey, dostupnye v RF. [Modern methods of treatment of patients with drug-resistant epilepsy available in the Russian Federation]. Zh. Epilepsiya i paroksizmal'nye sostoyaniya. 2016; 8(1): 22–8. (In Russian).
26. Ayvazyan S.O., Luk'yanova E.G., Shiryaev Yu.S. Sovremennye vozmozhnosti lecheniya farmakorezistentnoy epilepsii u detey. [Modern options for the treatment of drug-resistant epilepsy in children]. Zh. Epilepsiya i paraksizmal'nye sostoyaniya. 2014; 6(1): 34–42. (In Russian).
27. Olson C.A., Iñiguez A.J., Yang G.E. et al. Alterations in the gut microbiota contribute to cognitive impairment induced by the ketogenic diet and hypoxia. Cell Host Microbe. 2021; 29(9): 1378–92.
28. Verrotti A., Iapadre G., Di Francesco L. et al. Diet in the Treatment of Epilepsy: What We Know So Far. Nutrients. 2020; 12(9): 2645.
29. Mahapatra S., Nagpal R., Marya C.M. et al. Gut Mycobiome and Its Interaction With Diet, Gut Bacteria and Alzheimer's Disease Markers in Subjects With Mild Cognitive Impairment: A Pilot Study. EBioMedicine. 2020; 59: 102950.
30. Guzel O., Uysal U., Arslan N. Efficacy and Tolerability of Olive Oil-Based Ketogenic Diet in Children With Drug-Resistant Epilepsy: A Single Center Experience From Turkey. Eur J Paediatr Neurol. 2019; 23: 143–51.
31. Tyul'ganova D.A., Nasaev Sh.Sh., Chugreev I.A. i dr. Mekhanizmy deystviya ketogennoy diety. [Mechanisms of action of the ketogenic diet]. Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova. Spetsvypuski. 2018; 118(10-2): 72–5. (In Russian).
32. Sondhi V., Agarwala A., Pandey R.M. et al. Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy: A Randomized Clinical Trial. JAMA Pediatr. 2020; 174: 944–51.
33. Ding M., Lang Y., Shu H. et al. Microbiota-Gut-Brain Axis and Epilepsy: A Review on Mechanisms and Potential Therapeutics. Front Immunol. 2021; 12: 742449.
34. Rogawski M.A., Löscher W., Rho J.M. Mechanisms of action of antiseizure drugs and the ketogenic diet. Cold Spring Harb Perspect Med. 2016; 6(5).
35. Ivannikova E.V., Altashina M.V., Troshina E.A. Ketogennaya dieta: istoriya vozniknoveniya, mekhanizm deystviya, pokazaniya. [Ketogenic diet: history of occurrence, mechanism of action, indications]. Problemy Endokrinologii. 2022; 68(1): 49–72. (In Russian).
36. Yuskaitis C.J., Modasia J.B., Schrötter S. et al. DEPDC5-dependent mTORC1 signaling mechanisms are critical for the anti-seizure effects of acute fasting. Cell Rep. 2022; 40: 111278.
37. Greene A.E., Todorova M.T., McGowan R., Seyfried T.N. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. Epilepsia. 2001; 42: 1371–8.
38. Mantis J.G., Centeno N.A., Todorova M.T. et al. Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: Role of glucose and ketone bodies. Nutr. Metab. 2004; 1: 11.
39. Landgrave-Gómez J., Mercado-Gómez O.F., Vázquez-García M. et al. Anticonvulsant Effect of Time-Restricted Feeding in a Pilocarpine-Induced Seizure Model: Metabolic and Epigenetic Implications. Front. Cell Neurosci. 2016; 10: 7.

40. Taha A.Y., Burnham W.M., Auvin S. Polyunsaturated Fatty Acids and Epilepsy. Epilepsia. 2010; 51: 1348–58.
41. Bough K.J., Rho J.M. Anticonvulsant Mechanisms of the Ketogenic Diet. Epilepsia. 2007; 48: 43–58.
42. Zimmer L., Delpal S., Guilloteau D. et al. Chronic N-3 Polyunsaturated Fatty Acid Deficiency Alters Dopamine Vesicle Density in the Rat Frontal Cortex. Neurosci Lett. 2000; 284: 25–8.
43. Bahagat K.A., Elhady M., Aziz A.A. et al. Omega-6/Omega-3 Ratio and Cognition in Children With Epilepsy. Pediatr (Engl Ed). 2019; 91: 88–95.
44. Sohouli M.H., Razmpoosh E., Zarrati M., Jaberzadeh S. The Effect of Omega-3 Fatty Acid Supplementation on Seizure Frequency in Individuals With Epilepsy: A Systematic Review and Meta-Analysis. Nutr Neurosci. 2021; 30: 1–10.
45. Rho J.M., Shao L.R., Stafstrom C.E. 2-Deoxyglucose and Beta-Hydroxybutyrate: Metabolic Agents for Seizure Control. Front. Cell Neurosci. 2019; 13: 172.
46. Olson C.A., Vuong H.E., Yano J.M. et al. The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. Cell. 2018; 173(7): 1728–41.
47. Xie G., Zhou Q., Qiu C.Z. et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J. Gastroenterol. 2017; 23: 6164–71.
48. Amlerova J., Šroubek J., Angelucci F., Hort J. Evidences for a Role of Gut Microbiota in Pathogenesis and Management of Epilepsy. Int J Mol Sci. 2021; 22(11): 5576.
49. Rutsch A., Kantsjö J.B., Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. Front Immunol. 2020; 11: 604179.
50. Gershon M.D. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013; 20: 14–21.
51. Glebov K., Löchner M., Jabs R. et al. Serotonin stimulates secretion of exosomes from microglia cells. Glia. 2015; 63: 626–34.
52. Rothhammer V., Borucki D.M., Tjon E.C. et al. Microglial control of astrocytes in response to microbial metabolites. Nature. 2018; 557: 724–8.
53. Sudo N., Chida Y., Aiba Y. et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice J Physiol . 2004; 558(Pt 1): 263–75.
54. Cryan J.F., O'Riordan K.J., Cowan CSM. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019; 99(4): 1877–2013.
55. Chen Y., Xu J., Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders Nutrients. 2021; 13(6): 2099.
56. Cowan CSM., Hoban AE., Ventura-Silva AP. et al. Gutsy Moves: The Amygdala as a Critical Node in Microbiota to Brain Signaling. Bioessays. 2018; 40(1).
57. Galland L. The Gut Microbiome and the Brain. J Med Food. 2014; 17: 1261–72.
58. Frost G., Sleeth M.L., Sahuri-arisoylu M. et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat Commun. 2014; 5: 1–11.
59. Li D., Bai X., Jiang Y., Cheng Y. Butyrate Alleviates PTZ-Induced Mitochondrial Dysfunction, Oxidative Stress and Neuron Apoptosis in Mice via Keap1/Nrf2/HO-1 Pathway. Brain Res Bull. 2021; 168: 25–35.
60. Oleskin A.V., Shenderov B.A. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microb Ecol Health Dis. 2016; 2235: 1–12.
61. Nankova B.B., Agarwal R., MacFabe D.F., La Gamma E.F. Enteric Bacterial Metabolites Propionic and Butyric Acid Modulate Gene Expression, Including CREB-Dependent Catecholaminergic Neurotransmission, in PC12 Cells — Possible Relevance to Autism Spectrum Disorders. PloS One. 2014; 9: e103740.
62. Tolhurst G., Heffron H., Lam Y.S. et al. Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein–Coupled Receptor FFAR2. Diabetes. 2012; 61: 364–71.
63. Everard A., Lazarevic V., Gaïa N. et al. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. ISME J. 2014; 8: 2116–30.
64. Caspani G., Swann J. Small talk: Microbial metabolites involved in the signaling from microbiota to brain. Curr. Opin. Pharmacol. 2019; 48: 99–106.

ЛИТЕРАТУРА

1. Ерофеев Н.П., Радченко В.Г., Селиверстов П.В. Клиническая физиология толстой кишки. Механизмы действия короткоцепочечных жирных кислот в норме и при патологии. СПб.; 2012.
2. Воронкова К.В. Эпилепсии в практике педиатра. Практика педиатра. 2015; 1: 54–63.
3. Гузева О.В., Гузева В.И., Гузева В.В. и др. Результаты оценки качества лечения и жизни детей с эпилепсией. Педиатр. 2017; 2.
4. Beghi E., Giussani G., Abd-Allah F.A. et al. Global, Regional, and National Burden of Epilepsy, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019; 18: 357–75.
5. Dahlin M., Prast-Nielsen S. The gut microbiome and epilepsy. EBioMedicine. 2019; 44: 741–6.
6. Kobow K., Blümcke I. Epigenetics in Epilepsy. Neurosci Lett. 2018; 667: 40–6.

7. Wheless J.W. History of the ketogenic diet Epilepsia. 2008; 49(8): 3–5.
8. Meira I. D'Andrea, Romão T.T., Pires do Prado H.J. et al. Ketogenic Diet and Epilepsy: What We Know So Far. Front. Neurosci. 2019; 13: 5.
9. Lobo F., Haase J., Brandhorst S. The Effects of Dietary Interventions on Brain Aging and Neurological Diseases. Nutrients. 2022; 14(23): 5086.
10. Dyńka D., Kowalcze K., Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases. Nutrients. 2022; 14(23): 5003.
11. Клинические рекомендации. Эпилепсия и эпилептический статус у взрослых и детей. МЗ РФ. 2022.
12. Kossoff E.H., Zupec-Kania B.A., Auvin S. et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018; 3(2): 175–92.
13. Барановский А.Ю. Диетология: руководство. СПб.: Питер; 2012.
14. Педиатрия. Национальное руководство. Под ред. А.А. Баранова. М.: ГЭОТАР-Медиа. 2009; 1.
15. Ramm-Pettersen A., Selmer K.K., Nakken K.O. Glucose transporter protein type 1 (GLUT-1) deficiency syndrome. Tidsskr Nor Laegeforen. 2011; 131(8): 828–31.
16. Лукьянова Е.Г., Айвазян С.О., Осипова К.В. и др. Опыт применения кетогенной диеты у пациентов с синдромом дефицита транспортера глюкозы 1 типа (клиническое наблюдение). Журнал неврологии и психиатрии им. С.С.Корсакова 2015; 115(5-2): 53–60.
17. van der Louw E., van den Hurk D., Neal E. et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol. 2016; 20(6): 798–809.
18. Ye F., Li X.J., Jiang W.L. et al. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015; 11(1): 26–31.
19. Martin K., Jackson C.F., Levy R.G., Cooper P.N. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2016.
20. Neal E.G., Chaffe H., Schwartz R.H. et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008; 7(6): 500–6.
21. Lambrechts DAJE., de Kinderen RJA., Vles JSH. et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017; 135(2): 231–9.
22. Zare M., Okhovat A.A., Esmaillzadeh A. et al. Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial. Iran. J. Neurol. 2017; 16: 72–7.
23. Liu H., Yang Y., Wang Y. et al. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. Epilepsia Open. 2018; 3(1): 9–17.
24. Лукьянова Е.Г., Айвазян С.О., Осипова К.В. и др. Когнитивные и моторные функции у детей с фармакорезистентными формами эпилепсии, находящихся на кетогенной диете. Эпилепсия и пароксизмальные состояния. 2016; 8(1): 37–42.
25. Айвазян С.О., Ширяев Ю.С. Современные методы лечения пациентов с фармакорезистентной эпилепсией, доступные в РФ. Эпилепсия и пароксизмальные состояния. 2016; 8(1): 22–8.
26. Айвазян С.О., Лукьянова Е.Г., Ширяев Ю.С. Современные возможности лечения фармакорезистентной эпилепсии у детей. Эпилепсия и пароксизмальные состояния. 2014; 6(1): 34–42.
27. Olson C.A., Iñiguez A.J., Yang G.E. et al. Alterations in the gut microbiota contribute to cognitive impairment induced by the ketogenic diet and hypoxia. Cell Host Microbe. 2021; 29(9): 1378–92.
28. Verrotti A., Iapadre G., Di Francesco L. et al. Diet in the Treatment of Epilepsy: What We Know So Far. Nutrients. 2020; 12(9): 2645.
29. Mahapatra S., Nagpal R., Marya C.M. et al. Gut Mycobiome and Its Interaction With Diet, Gut Bacteria and Alzheimer's Disease Markers in Subjects With Mild Cognitive Impairment: A Pilot Study. EBioMedicine. 2020; 59: 102950.
30. Guzel O., Uysal U., Arslan N. Efficacy and Tolerability of Olive Oil-Based Ketogenic Diet in Children With Drug-Resistant Epilepsy: A Single Center Experience From Turkey. Eur J Paediatr Neurol. 2019; 23: 143–51.
31. Тюльганова Д.А., Насаев Ш.Ш., Чугреев И.А. и др. Механизмы действия кетогенной диеты. Журнал неврологии и психиатрии им. С.С. Корсакова. Спецвыпуски. 2018; 118(10-2): 72–5.
32. Sondhi V., Agarwala A., Pandey R.M. et al. Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy: A Randomized Clinical Trial. JAMA Pediatr. 2020; 174: 944–51.
33. Ding M., Lang Y., Shu H. et al. Microbiota-Gut-Brain Axis and Epilepsy: A Review on Mechanisms and Potential Therapeutics. Front Immunol. 2021; 12: 742449.
34. Rogawski M.A., Löscher W., Rho J.M. Mechanisms of action of antiseizure drugs and the ketogenic diet. Cold Spring Harb Perspect Med. 2016; 6(5).
35. Иванникова Е.В., Алташина М.В., Трошина Е.А. Кетогенная диета: история возникновения, механизм действия, показания. Проблемы эндокринологии. 2022; 68(1): 49–72.

36. Yuskaitis C.J., Modasia J.B., Schrötter S. et al. DEPDC5-dependent mTORC1 signaling mechanisms are critical for the anti-seizure effects of acute fasting. Cell Rep. 2022; 40: 111278.
37. Greene A.E., Todorova M.T., McGowan R., Seyfried T.N. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. Epilepsia. 2001; 42: 1371–8.
38. Mantis J.G., Centeno N.A., Todorova M.T. et al. Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: Role of glucose and ketone bodies. Nutr. Metab. 2004; 1: 11.
39. Landgrave-Gómez J., Mercado-Gómez O.F., Vázquez-García M. et al. Anticonvulsant Effect of Time-Restricted Feeding in a Pilocarpine-Induced Seizure Model: Metabolic and Epigenetic Implications. Front. Cell Neurosci. 2016; 10: 7.
40. Taha A.Y., Burnham W.M., Auvin S. Polyunsaturated Fatty Acids and Epilepsy. Epilepsia. 2010; 51: 1348–58.
41. Bough K.J., Rho J.M. Anticonvulsant Mechanisms of the Ketogenic Diet. Epilepsia. 2007; 48: 43–58.
42. Zimmer L., Delpal S., Guilloteau D. et al. Chronic N-3 Polyunsaturated Fatty Acid Deficiency Alters Dopamine Vesicle Density in the Rat Frontal Cortex. Neurosci Lett. 2000; 284: 25–8.
43. Bahagat K.A., Elhady M., Aziz A.A. et al. Omega-6/Omega-3 Ratio and Cognition in Children With Epilepsy. Pediatr (Engl Ed). 2019; 91: 88–95.
44. Sohouli M.H., Razmpoosh E., Zarrati M., Jaberzadeh S. The Effect of Omega-3 Fatty Acid Supplementation on Seizure Frequency in Individuals With Epilepsy: A Systematic Review and Meta-Analysis. Nutr Neurosci. 2021; 30: 1–10.
45. Rho J.M., Shao L.R., Stafstrom C.E. 2-Deoxyglucose and Beta-Hydroxybutyrate: Metabolic Agents for Seizure Control. Front. Cell Neurosci. 2019; 13: 172.
46. Olson C.A., Vuong H.E., Yano J.M. et al. The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet. Cell. 2018; 173(7): 1728–41.
47. Xie G., Zhou Q., Qiu C.Z. et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. World J. Gastroenterol. 2017; 23: 6164–71.
48. Amlerova J., Šroubek J., Angelucci F., Hort J. Evidences for a Role of Gut Microbiota in Pathogenesis and Management of Epilepsy. Int J Mol Sci. 2021; 22(11): 5576.
49. Rutsch A., Kantsjö J.B., Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. Front Immunol. 2020; 11: 604179.
50. Gershon M.D. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013; 20: 14–21.
51. Glebov K., Löchner M., Jabs R. et al. Serotonin stimulates secretion of exosomes from microglia cells. Glia. 2015; 63: 626–34.
52. Rothhammer V., Borucki D.M., Tjon E.C. et al. Microglial control of astrocytes in response to microbial metabolites. Nature. 2018; 557: 724–8.
53. Sudo N., Chida Y., Aiba Y. et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice J Physiol . 2004; 558(Pt 1): 263–75.
54. Cryan J.F., O'Riordan K.J., Cowan CSM. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019; 99(4): 1877–2013.
55. Chen Y., Xu J., Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders Nutrients. 2021; 13(6): 2099.
56. Cowan CSM., Hoban AE., Ventura-Silva AP. et al. Gutsy Moves: The Amygdala as a Critical Node in Microbiota to Brain Signaling. Bioessays. 2018; 40(1).
57. Galland L. The Gut Microbiome and the Brain. J Med Food. 2014; 17: 1261–72.
58. Frost G., Sleeth M.L., Sahuri-arisoylu M. et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat Commun. 2014; 5: 1–11.
59. Li D., Bai X., Jiang Y., Cheng Y. Butyrate Alleviates PTZ-Induced Mitochondrial Dysfunction, Oxidative Stress and Neuron Apoptosis in Mice via Keap1/Nrf2/HO-1 Pathway. Brain Res Bull. 2021; 168: 25–35.
60. Oleskin A.V., Shenderov B.A. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microb Ecol Health Dis. 2016; 2235: 1–12.
61. Nankova B.B., Agarwal R., MacFabe D.F., La Gamma E.F. Enteric Bacterial Metabolites Propionic and Butyric Acid Modulate Gene Expression, Including CREB-Dependent Catecholaminergic Neurotransmission, in PC12 Cells — Possible Relevance to Autism Spectrum Disorders. PloS One. 2014; 9: e103740.
62. Tolhurst G., Heffron H., Lam Y.S. et al. Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein–Coupled Receptor FFAR2. Diabetes. 2012; 61: 364–71.
63. Everard A., Lazarevic V., Gaïa N. et al. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. ISME J. 2014; 8: 2116–30.
64. Caspani G., Swann J. Small talk: Microbial metabolites involved in the signaling from microbiota to brain. Curr. Opin. Pharmacol. 2019; 48: 99–106.

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COLONIZATION RESISTANCE AND INTESTINAL MICROBIOTA AS FACTORS OF COUNTERACTION TO THE DEVELOPMENT OF INTESTINAL INFECTIONS (REVIEW)

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Abstract. With the continuing trend of increasing incidence of acute intestinal infections in children in early childhood in recent years, the importance of bacterial pathogens of opportunistic nature has remained. The issues of etiological and epidemiological significance of opportunistic enterobacteria in children without signs of immunodeficiency remain unresolved. There are many levels of protection of the human body from pathogens, which are realized through direct mechanisms of interaction between microbes, and indirect mechanisms mediated by stimulation of the immune system of the mucous membrane by indigenous representatives of the microbiota. Bacteriocins of commensal bacteria can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract. Colonization resistance of intestinal mucous membranes and colonization activity of microbes are directly opposite, but interrelated processes. Opportunistic enterobacteria acquire pathogenicity properties and become dangerous pathogens of infectious diarrhea under certain conditions that are created when the properties of the environment change. The intestinal microbiota, depending on its condition, is actively involved in the prevention, but sometimes also in provoking diarrheal diseases. Currently, *Klebsiella pneumoniae* plays a leading role among the opportunistic pathogens of intestinal infections of community-acquired origin in children of the first three years of life.

Key words: *acute intestinal infections; opportunistic enterobacteria; early childhood; colonization resistance of the intestine; microbiota; Klebsiella pneumoniae.*

КОЛОНИЗАЦИОННАЯ РЕЗИСТЕНТНОСТЬ И МИКРОБИОТА КИШЕЧНИКА КАК ФАКТОРЫ ПРОТИВОДЕЙСТВИЯ РАЗВИТИЮ КИШЕЧНЫХ ИНФЕКЦИЙ (ОБЗОР)

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Резюме. При сохраняющейся тенденции роста заболеваемости детей острыми кишечными инфекциями в раннем детском возрасте в последние годы сохраняется значение бактериальных возбудителей условно-патогенной природы. Вопросы этиологической и эпидемиологической значимости условно-патогенных энтеробактерий у детей, не имеющих признаков иммунодефицита, остаются нерешенными. Существует множество уровней защиты организма человека от патогенов, которые реализуются за счет прямых механизмов взаимодействия между микробами и косвенных механизмов, опосредованных стимуляцией иммунной системы слизистой оболочки индигенными представителями микробиоты. Бактериоцины комменсальных бактерий могут ингибировать патогенные и условно-патогенные микроорганизмы, участвуя в формировании структуры микробиоты желудочно-кишечного тракта. Колонизационная резистентность слизистых оболочек кишечника и колонизационная активность микробов представляют собой прямо противоположные, но взаимосвязанные процессы. Условно-патогенные энтеробактерии приобретают свойства патогенности и становятся опасными возбудителями инфекционных диарей при определенных условиях, которые создаются при изменении свойств среды. Микробиота кишечника в зависимости от своего состояния активно участвует в предотвращении, но иногда и в провоцировании диарейных заболеваний. В настоящее время среди условно-патогенных возбудителей кишечных инфекций внебольничного происхождения у детей первых трех лет жизни лидирующая роль принадлежит *Klebsiella pneumoniae.*

Ключевые слова: *острые кишечные инфекции; условно-патогенные энтеробактерии; ранний детский возраст; колонизационная резистентность кишечника; микробиота; Klebsiella pneumoniae.*

INTRODUTION

With the continuing trend of increasing incidence of acute intestinal infections (AII) in the population of the Russian Federation in the last 10–20 years [1, 2], the high epidemic significance of viral diarrhea in children [3, 4], and a marked decrease in the incidence of shigellosis among children, the importance of AII of opportunistic etiology is retained [5]. A high proportion of AIIs associated with opportunistic representatives of the microbiota (the proportion of AIIs of established bacterial etiology without specifying the pathogen in the total AIIs) is noted in the Astrakhan Region (81.2%), the Republic of Crimea (62.7%), and the Volgograd Region (59.4%), the Republic of Tyva (53.3%) (the national average is 12.8%), which may indicate an insufficient level of implementation of modern methods of laboratory etiological diagnosis [1, 6].

The microbiota in individuals with reduced immunological reactivity is in a state of dysbiosis, in which it is possible to replace indigenous microbial biofilms with polymicrobial biofilms of opportunistic microorganisms that protect them from the effects of innate immunity. As a result, a local infectious process is formed, which, under certain conditions, can become a generalized form by intestinal translocation of microorganisms and their toxins into the lymphatic channel and bloodstream [7, 8].

Currently, the issues of the etiological and epidemiological significance of opportunistic enterobacteria in AII in pediatric patients without the signs of immunodeficiency still remain unresolved.

MECHANISMS PROVIDING RESISTANCE TO COLONIZATION OF THE INTESTINAL MUCOSA

The integrative function of the intestine the protection of the body from pathogens and their translocation to other biotopes is associated with colonization resistance associated with the microbial-tissue complex — an evolutionarily established multifunctional union consisting of the microbiota of the parietal zone of the mucous membrane and underlying tissue structures [9].

"Colonization resistance" is associated with a stable and diverse microbiota in tandem with the absence of inflammation and involves specific interactions between the mucosal immune system and commensal microbes [10]. During all periods of life, the effectiveness of colonization resistance is determined by the optimal quantitative and qualitative composition of the microbiota [11].

The formation of intestinal microbiota begins during the prenatal period; in ontogenesis is a long-term multifactorial process, the violation of which is fraught with the development of various pathological conditions [12]. The formation of the microbiota continues until the child is 7 years of age; its composition is controlled by specific (immune) and non-specific mechanisms [13]. The intestinal microbiota, being the most autonomous and stable microbial community, dominates in quantitative and functional terms compared to that in other biotopes and maintains the required level of immunological reactivity of the organism. The maximum number of bacterial cells (about 10^{14}) lives in the

large intestine, which is tens of times greater than the total number of cells in the human body. In total, from 400 to 1500 species of microbes live in the digestive tract, and the total genome of bacteria contains about 3 million genes, 150 times the size of the genome of the macroorganism [13, 14]. The functional orientation and density of indigenous microbiota is unequal in the upper and lower parts of the digestive tract [15]. The proximal parts of the large intestine are inhabited by microbes attached to the intestinal chyme, the transverse region is inhabited by planktonic bacteria, and the distal parts are inhabited by bacteria associated with the mucous membrane [16]. The main metabolites of the intestinal microbiome, acting at the local level and in the periphery, are short-chain fatty acids (SCFAs) formed during the fermentation of dietary fiber, causing immune, endocrine and neuronal responses due to numerous SCFA receptors [17–19].

Resistance to colonization by bacterial pathogens is one of the most obvious functions of the human intestinal microbiota [20]. Disturbances in the composition of the microbiota reduce colonization resistance and increase the body's susceptibility to intestinal infection. The subtle mechanisms that provide resistance to colonization of the intestinal mucosa, even by fairly well-known and common pathogens, remain poorly understood. Using an experimental model of coli infection in piglets caused by enterotoxigenic strains (ETEC), methods of metagenomics and 16S rRNA sequencing showed that in the fecal microbiota of individuals with developed diarrhea, compared with individuals resistant to this infection, the ratio of *Bacteroides/Firmicutes* (B/F) was significantly lower (Fig. 1). In the jejunum of piglets with diarrhea, an increased percentage of *Lactococcus* (belonging to *Firmicutes)* was detected, and in the feces — a decreased percentage of *Prevotella* (belonging to *Bacteroides*) and an increased percentage of *Escherichia-Shigella*. However, the role of *Lactococcus* and *Prevotella* in the pathogenesis of diarrhea caused by ETEC has not yet been determined [21].

There is evidence of direct and indirect inhibition of some enteric pathogens by host systems [22]. Secondary bile acids (deoxycholic, lithocholic, ursodeoxycholic, allocholic), short-chain fatty acids (acetic, propionic, butyric) and bacteriocins, the production of which depends on the state of the microbiota, as well as the intestinal mucosal and epithelial barriers and competition of microbiota for nutrient substrates with pathogens, are considered as factors for direct inhibition of intestinal colonization. Short-chain fatty acids function as communication between the microbiota and the intestinal epithelium, as well as between different representatives of the microbiota [23].

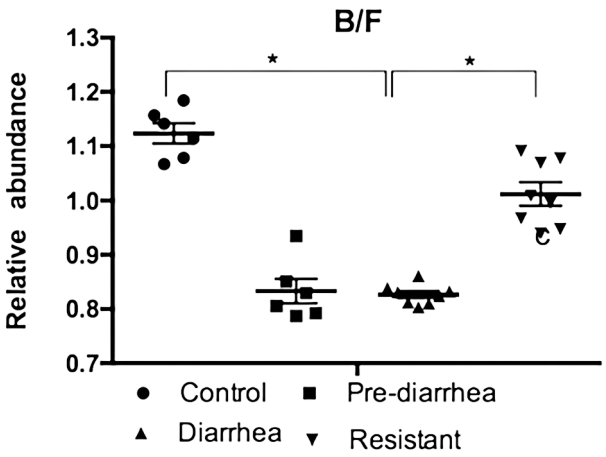

Fig. 1. Analysis of the relative abundance of *Bacteroidetes* (B) and *Firmicutes* (F) in feces using real-time PCR in the control group of piglets (Control), piglets with pre-diarrhea (Pre-diarrhea), those who developed diarrhea (Diarrhea) and those resistant to diarrhea piglets (Resistant) (* — p <0.05, one-way ANOVA) [21]

Рис. 1. Анализ относительной численности *Bacteroidetes* (B) и *Firmicutes* (F) в кале методом ПЦР в режиме реального времени у контрольной группы поросят (Control), поросят с пред-диареей (Pre-diarrhea), развившейся диареей (Diarrhea) и резистентных к диарее поросят (Resistant) (* — p <0,05, односторонний ANOVA) [21]

Indirect inhibition of intestinal colonization by pathogens is carried out by the innate immune system, which plays the role of protection against infectious agents and maintaining tissue homeostasis. The commensal intestinal microbiota and its components, through pattern recognition receptors, maintain the innate immune system in a state of physiological tone due to the balance of the synthesis of pro-inflammatory and anti-inflammatory cytokines and antimicrobial substances [24]. Thus, commensal intestinal microbiota induces the differentiation of CD4 T cells to Th17, which promote resistance colonization of pathogens by releasing the cytokine IL-22. Inhibition of colonization of pathogens is carried out under the influence of antimicrobial peptides, sIgA and other tissue factors of mucous membrane inflammation (Fig. 2) [22].

The relationship between changes in the microbiota and the reactions of the immune system has been established in the normal and reduced states of colonization resistance of the intestinal mucosa. In other words, there are many levels of host protection from pathogens, which are rea-

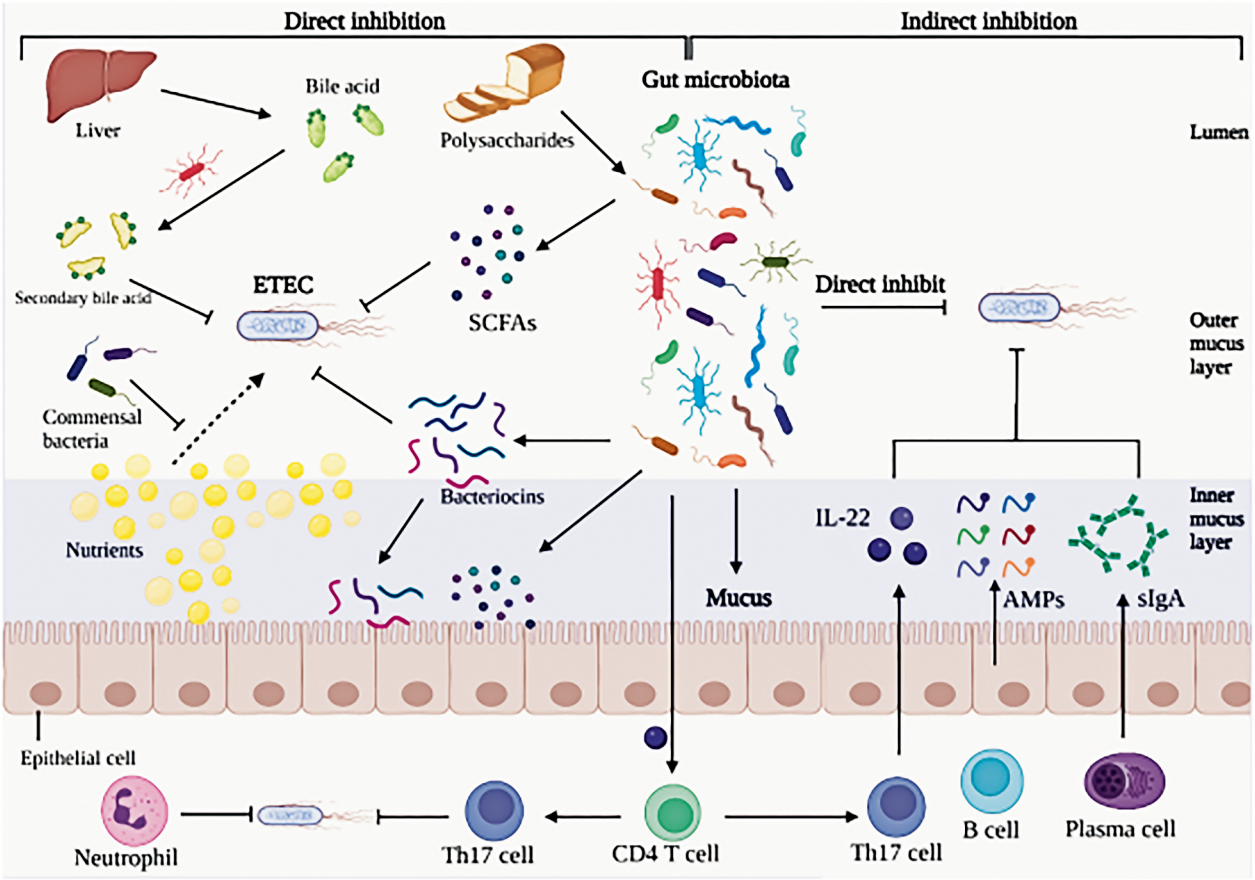

Fig. 2. Mechanisms of direct and indirect inhibition of intestinal colonization by the causative agent of ETEC infection, mediated by intestinal microbiota [22]

Рис. 2. Механизмы прямого и непрямого ингибирования колонизации кишечника возбудителем ETEC-инфекции, опосредованного микробиотой кишечника [22]

lized through direct mechanisms of interaction between microbes, as well as indirect mechanisms mediated by stimulation of the mucosal immune system by representatives of the commensal microbiota that maintain health [10].

INTERACTION BETWEEN BACTERIOCINS OF INTESTINAL MICROBIOTA AND THE IMMUNE SYSTEM

Numerous studies have shown that bacteriocins of commensal microbiota can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract (GIT) and other ecological niches of the body (Fig. 3) [25, 26].

The inhibitory effects of various bacteriocins against pathogens responsible for nosocomial intestinal infections have been proven [27]. Bacteriocins can be used as growth inhibitors of *Enterobacteriaceae* with multiple resistance to antibiotics, including *K. pneumoniae*, *Acinetobacter* spp. and others [28]. Microcin J25, a Gram-negative bacteriocin, exhibits high inhibitory activity against Salmonella and Escherichia coli, which are multi-resistant to antimicrobial drugs [29]. The sites of application of most bacteriocins are in the distal parts of the small intestine and in the colon [30]. The absorption of bacteriocins through the gastrointestinal epithelium and vascular endothelium into the bloodstream has been described [31]. Administration of bacteriocins to mice led to the increase in the number of blood macrophages/monocytes and antibody production due to modulation of the activity of antigen-presenting cells [32].

Antimicrobial molecules produced by commensal microbiota — bacteriocins and SCFAs-strengthen the barrier function of the epithelium by penetrating the inner mucus layer covering the epithelium, providing colonization resistance [22, 33]. In response to the effects of infectious agents, dynamic changes in the intestinal mucosal barrier occur. The rate of mucin secretion is regulated by innate and adaptive immunity. Infection of the

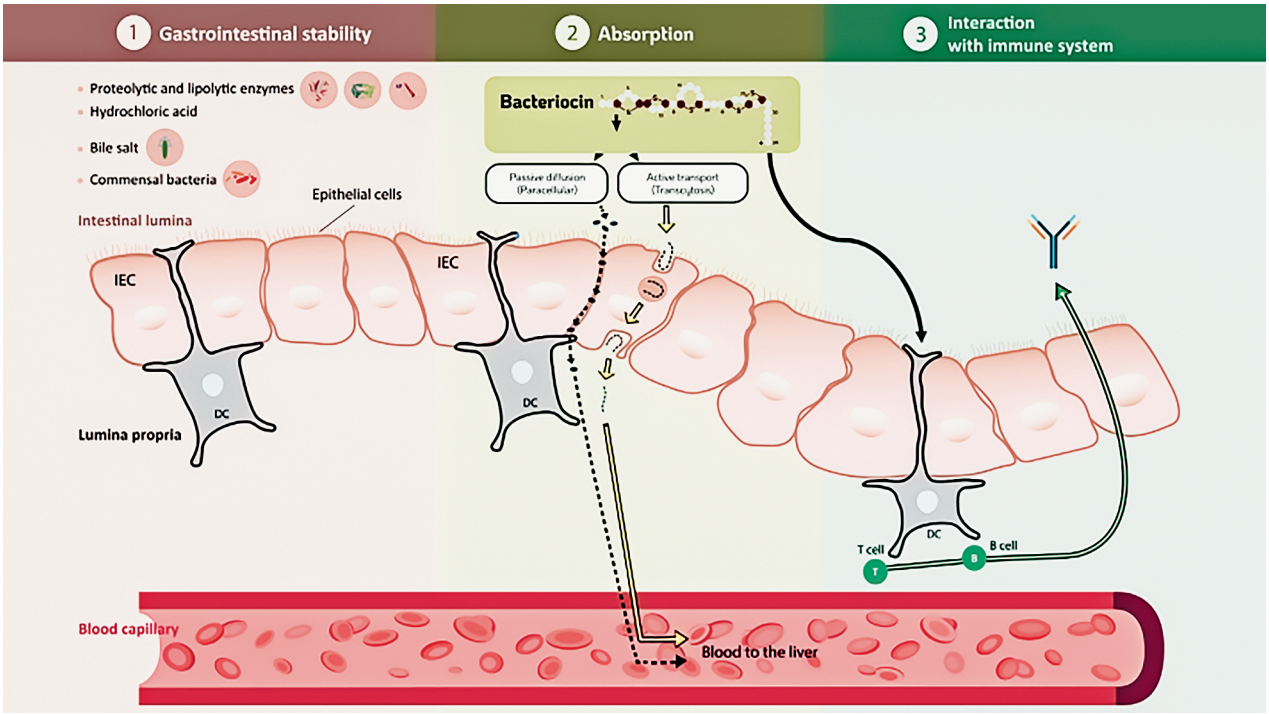

Fig. 3. Interaction of bacteriocins with the gastrointestinal tract and the immune system: 1 — stability of the gastrointestinal tract, including enzyme activity, pH changes, commensal bacteria; 2 — pathways for absorption of bacteriocins by epithelial cells; 3 — interaction of bacteriocins with the immune system [25]

Рис. 3. Взаимодействие бактериоцинов с ЖКТ и иммунной системой: 1 — стабильность состояния ЖКТ, включая активность ферментов, изменения pH, комменсальные бактерии; 2 — пути всасывания бактериоцинов эпителиальными клетками; 3 — взаимодействие бактериоцинов с иммунной системой [25]

intestinal mucosa by pathogens is accompanied by hyperproduction of mucus, antimicrobial molecules and specific immunoglobulins; the rate of their production is influenced by inflammatory factors and microbiota [34].

However, more in-depth studies combining metagenomic and metabolomic approaches are needed to detail the effects of microbial bacteriocins on the composition and balance of the intestinal microbiota [25].

COLONIZATION RESISTANCE AND INTESTINAL MICROBIOTA

Colonization resistance of the intestinal mucosa and colonization activity of microbes are directly opposite, but interrelated processes. Short-chain fatty acids (SCFAs), secreted by bacterial members of the intestinal microbiota, optimize the properties of the intestinal environment. In the case of inflammatory bowel disease, SCFA levels typically decrease, accompanied by an increase in opportunistic adherent-invasive *E. coli* (AIEC). And therefore, SCFA drugs are sometimes prescribed for the treatment of inflammatory bowel diseases [35]. At the same time, the results of a number of studies have shown that SCFAs can enhance the virulence of enterobacteria. It turned out that propionate and butyrate increase the expression of the virulence genes of AIEC, while strengthening the epithelial barrier and reducing the severity of inflammation. Research data show that increasing the colonization activity of the opportunistic pathogen of AII, namely AIEC, due to increased virulent properties, leads to overcoming colonization resistance of the intestinal mucosa [23].

Opportunistic enterobacteria acquire pathogenic properties and become dangerous agents of infectious processes under certain conditions, which are often created when their habitat changes. Metabolites formed during the digestion of fiber can lead to the appearance of pathogenic properties in symbiotic representatives of bacteroids carrying glycoside hydrolases genes that break down starch and are activated in the presence of dietary fiber. For this reason, *B. thetaiotaomicron*, as well as *B. fragilis*, against the background of increasing resistance to antimicrobial peptides and proteins, are capable of enhancing adhesive properties, forming a biofilm, and causing dangerous opportunistic infections [36].

Commensal *E. coli* are exposed to a wide range of antimicrobial agents, which potentiates the increase in antibiotic resistance genes. Changes in the genetic characteristics of *E. coli* place it in the category of opportunistic pathogens causing urinary tract infections, neonatal meningitis, and bacteremia in immunocompetent patients. Contamination of food products by *E. coli*, which has multidrug resistance and high colonization activity, poses a danger to consumers due to the very possible development of infectious diarrhea [37, 38].

Thus, while it was previously believed that the microbiota served as a barrier to pathogens in intestinal infections, today the understanding of microbiota-mediated resistance to pathogens has evolved significantly. It is now clear that the microbiota, depending on its state, not only actively participates in the prevention, but sometimes also in the provocation of infectious diseases [39].

KLEBSIELLA PNEUMONIAE AS A CAUSATIVE AGENT OF NOSOCOMIAL AND COMMUNITY-ACQUIRED INTESTINAL INFECTION IN CHILDREN IN EARLY CHILDHOOD

Everyday practice shows that *Klebsiella pneumonia* plays a leading role among opportunistic pathogens of OCI of community-acquired origin in children of the first three years of life [40–42]. Traditionally, Klebsiella are considered opportunists because they cause infectious lesions of various locations in newborns, immunocompromised individuals and hospitalized patients [43, 44]. At

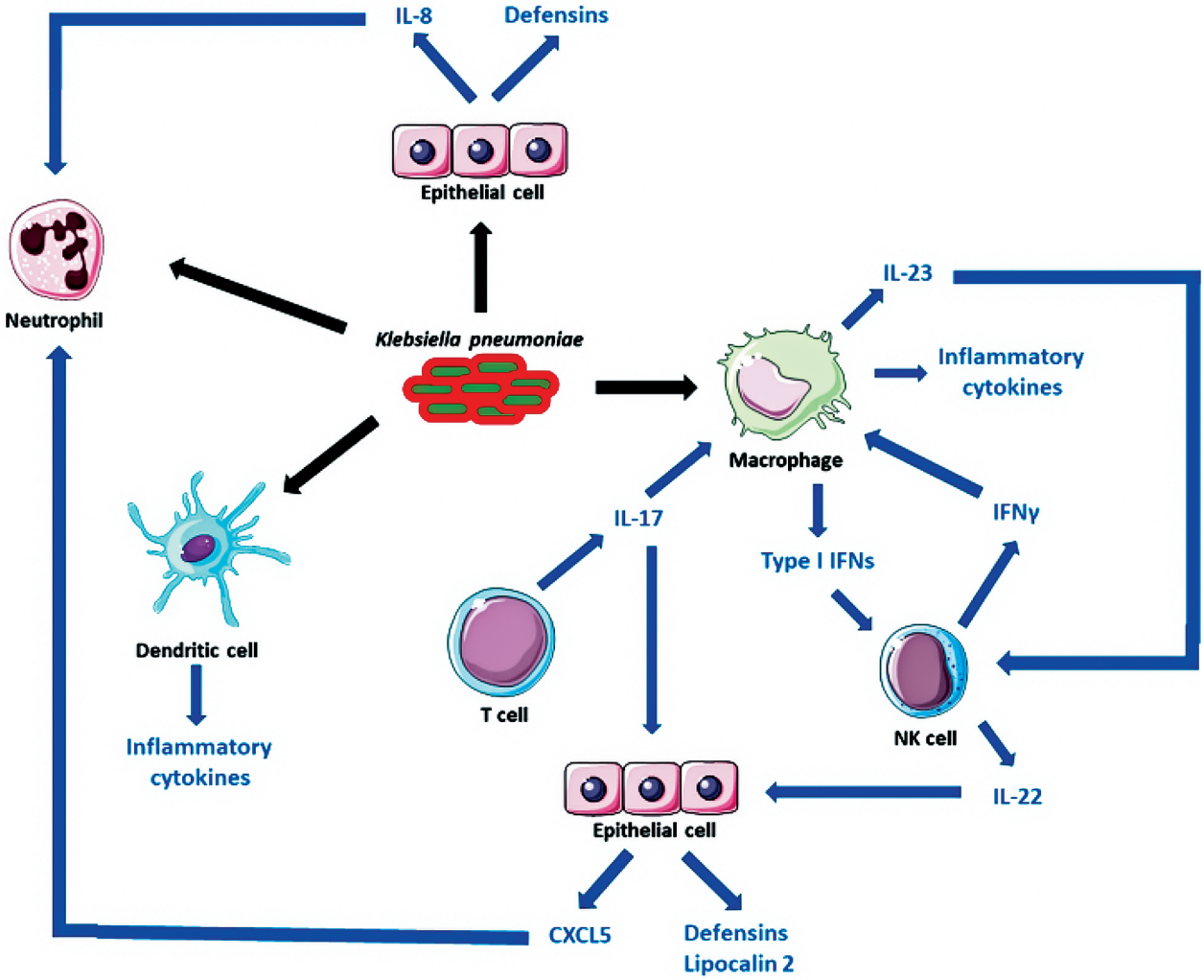

Fig. 4. Mechanisms of innate immunity to infections caused by *K. pneumoniae*. Interactions of *K. pneumoniae* with neutrophils, macrophages, dendritic and epithelial cells are indicated by black arrows; interactions with subpopulations of T cells and NK cells involved in bacterial clearance are indicated by blue arrows [47]

Рис. 4. Механизмы врожденного иммунитета к инфекциям, вызванным *K. pneumoniae*. Взаимодействия *K. pneumoniae* с нейтрофилами, макрофагами, дендритными и эпителиальными клетками отмечены черными стрелками; взаимодействия с субпопуляциями Т-клеток, NK-клеток, участвующими в бактериальном клиренсе, отмечены синими стрелками [47]

the same time, microbes of the genus Klebsiella are often found in the intestinal microbiota of healthy young children [13]. The outcome of colonization of children's intestines with Klebsiella depends on the presence of pathogenicity factors (capsule, lipopolysaccharide, siderophores, types 1 and 3 fimbriae, etc.), the level of contamination of the mucous membrane, colonization resistance, and immune activity (Fig. 4) [45–47].

The manifestation of AII caused by *K. pneumoniae* is a clinical expression of the insufficient effectiveness of the host defense mechanisms against pathogens [48]. The diagnosis of community-acquired AII caused by *K. pneumoniae* is established taking into account the detection of the pathogen in the stool in a high concentration (at least 5 lg CFU/g). And yet, the modern level of studying the biological properties of microorganisms indicates that a quantitative indicator does not always determine the ability of an isolate to cause a disease, the development of which is most associated with the realization of the pathogenic potential of the pathogen, ensuring its participation in the infectious process [49]. Indirect confirmation of the connection between the severity of the virulent properties of *K. pneumoniae* and the intensity of reproduction is the identification of an increase in resistance to ampicillin/sulbactam and to gentamicin with an increase in the concentration of the pathogen in fecal samples from children with AII [50]. Community-acquired cases of intestinal klebsiellosis in children of different ages suggest the possibility of contact, household and foodborne infection [51, 52]. It should be noted, however, that in a comparative aspect, the clinical and epidemiological characteristics of Klebsiella infections of community-acquired and nosocomial origin in children have not been sufficiently studied [53].

OPPORTUNISTIC ENTEROBACTERIA IN COMBINATION WITH VIRUSES IN INTESTINAL INFECTIONS IN CHILDREN

The scientific literature in young children describes combinations of Klebsiella infection with various opportunistic representatives of the *Enterobacteriaceae* family, including co-infections of *K. pneumoniae* with respiratory viruses [54]. Currently, against the backdrop of a widespread increase in co-infections, the issue of AII caused by a combination of opportunistic pathogens with intestinal viruses in children arises [55]. The results of studying the characteristics of clinical and laboratory signs of AII associated with *K. pneumonia* in young children show that the nature and severity of these signs are determined to a greater extent by the combination of *K. pneumoniae* with other opportunistic enterobacteria than by the combination of *K. pneumoniae* with intestinal viruses , thereby confirming the importance of the severity of background intestinal dysbiosis, which is involved in reducing the nonspecific resistance of the body. Identifying differences between mono- and co-infections associated with opportunistic agents may contribute to a more detailed understanding of the pathogenesis of diarrheal diseases.

Recent studies have established that the characteristics of the intestinal microbiome, along with the host genotype and the strength of local immunity, serve as interdependent key factors in the development of infectious diarrhea. In an *in vitro* experiment, it was demonstrated that the attachment of viral pathogens to host intestinal epithelial cells was negatively correlated with the abundance of certain groups of bacteria, such as *Faecalibacterium* and *Ruminococcus* spp., and sIgA titers to noro- and rotaviruses. The authors stated that there is a relationship between host genetics, intestinal microbiota and susceptibility to intestinal infections in humans [56]. Another experimental study demonstrated the preventive effect of using human milk oligosaccharides in rats for rotavirus diarrhea, due to the elimination of intestinal dysbiosis, as well as the immunomodulatory effect of oligosaccharides in the form of an increase in the expression of Toll-like receptors (TLRs), which confirms the active interaction of intestinal viruses with microbiota and the immune system [57].

A signature of pathogen-dependent intestinal dysbiosis based on microbiome analysis using 16S rRNA sequencing was identified in 80 patients with viral gastroenteritis in Ghana. A number of pathogens have been identified that are closely associated with viral diarrhea (*Escherichia-Shigella, Klebsiella and Campylobacter*). Co-infection with these pathogens and enteric viruses has been observed in several cases [58].

Many species of intestinal microbiota bacteria belonging to *Bacillus, Enterobacter, Enterococcus* and *Klebsiella* spp. secrete *enhancin-like proteins* that specifically damage membrane-bound mucins of the intestinal epithelium, leading to disruption of the integrity of the epithelial barrier and the development of viral infection. Deciphering the molecular mechanisms that regulate the interaction of microbiota, bacterial and viral pathogens will in the future become the basis for

the development of promising strategies to combat diarrheal infections [59].

Native-born authors, in experimental studies of the effectiveness of using a metaprebiotic that suppresses pathogens and stimulates the development of indigenous microbes producing antimicrobial exometabolites, on convection white mice, managed to prove the leading role of colonization resistance and normobiota of the digestive tract in ensuring the protection of the sensitive organism from pathogens of intestinal infections and in creating a selective microecological advantage, resisting infectious agents, as a result of bioincompatibility of the "host versus pathogen" type [60].

CONCLUSION

With the continuing trend of increasing incidence of AII in children in early childhood in recent years, the importance of bacterial pathogens of opportunistic nature has remained. The issues of etiological and epidemiological significance of opportunistic enterobacteria in children without signs of immunodeficiency remain unresolved. There are many levels of protection of the human body from pathogens, which are realized through direct mechanisms of interaction between microbes, and indirect mechanisms mediated by stimulation of the immune system of the mucous membrane by indigenous representatives of the microbiota. Bacteriocins of commensal bacteria can inhibit pathogenic and opportunistic microorganisms, participating in the formation of the structure of the microbiota of the gastrointestinal tract. Colonization resistance of intestinal mucous membranes and colonization activity of microbes are directly opposite, but interrelated processes. Opportunistic enterobacteria acquire pathogenicity properties and become dangerous pathogens of infectious diarrhea under certain conditions that are created when the properties of the environment change. The intestinal microbiota, depending on its condition, is actively involved in the prevention, but sometimes also in provoking diarrheal diseases. The intestinal microbiome ensures the resistance of the mucous membrane to the colonization of pathogens through the implementation of the following main functions: direct inhibition of pathogens through the production of antimicrobial compounds; maintaining the mucous barrier lining the intestinal epithelium; regulation of local and general immune response; effective use of exogenous and endogenous host nutrients by commensals. A holistic view that includes immunological and microbiological aspects of the intestinal ecosystem reflects the processes that contribute to maintaining intestinal homeostasis and resistance to colonization by pathogens. Currently, *Klebsiella pneumoniae* plays a leading role among the opportunistic pathogens of intestinal infections of community-acquired origin in children of the first three years of life.

ADDITIONAL INFORMATION

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

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

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

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REFERENCES

1. O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiyskoy Federatsii v 2022 godu: Gosudarstvennyy doklad. [On the state of sanitary and epidemiological well-being of the population in the Russian Federation in 2022: State report]. Moskva: Federal'naya sluzhba po nadzoru v sfere zashchity prav potrebiteley i blagopoluchiya cheloveka. 2023. (In Russian).
2. Sergevnin V.I. Sovremennyye tendentsii v mnogoletney dinamike zabolevayemosti ostrymi kishechnymi infektsiyami bakterial'noy i virusnoy etiologii. [Current trends in the long-term dynamics of the incidence of acute intestinal infections of bacterial and viral etiology]. Epidemiologiya i vaktsinoprofilaktika. 2020; 19(4): 14–9. (In Russian).

3. Karpovich G.S., Vasyunin A.V., Krasnova Ye.I., Degtyarev A.I. Epidemiologicheskiye i laboratornyye osobennosti kishechnykh infektsiy virusnoy etiologii u detey pervogo goda zhizni v Novosibirske. [Epidemiological and laboratory features of intestinal infections of viral etiology in children of the first year of life in Novosibirsk]. Sibirskiy meditsinskiy vestnik. 2020; 2: 35–40. (In Russian).
4. Kovalev O.B., Molochkova O.V., Konyayev K.S. i dr. Etiologiya i klinicheskiye proyavleniya ostrykh kishechnykh infektsiy u detey, po dannym statsionara za 2016–2018 gg. [Etiology and clinical manifestations of acute intestinal infections in children, according to hospital data for 2016–2018]. Detskiye infektsii. 2019; 18(2): 54–7. (In Russian).
5. Murzabayeva R.T., Mavzyutov A.R., Valishin D.A. Kliniko-immunologicheskiye paralleli pri ostrykh kishechnykh infektsiyakh, vyzvannykh uslovno-patogennymi enterobakteriyami. [Clinical and immunological parallels in acute intestinal infections caused by opportunistic enterobacteria]. Infektsionnyye bolezni. 2018; 16(4): 79–85. (In Russian).
6. Gonchar N.V., Yermolenko K.D., Klimova O.I. i dr. Bakterial'nyye kishechnyye infektsii s sindromom gemokolita u detey: etiologiya, laboratornaya diagnostika. [Bacterial intestinal infections with hemocolitis syndrome in children: etiology, laboratory diagnostics]. Meditsina ekstremal'nykh situatsiy. 2019; 1: 90–104. (In Russian).
7. Bondarenko V.M., Rybal'chenko O.V. Otsenka mikrobioty i probioticheskikh shtammov s pozitsiy novykh nauchnykh tekhnologiy. [Assessment of microbiota and probiotic strains from the perspective of new scientific technologies]. Farmateka. 2016; 11(324): 21–33. (In Russian).
8. Murphy C., Clegg S. Klebsiella pneumoniae and type 3 fimbriae: nosocomial infection, regulation and biofilm formation. Future Microbiol. 2012; 7 (8): 991–1002. DOI: 10.2217/fmb.12.74.
9. Minushkin O.N., Yelizavetina G.A., Ardatskaya M.D. Narusheniya balansa mikroflory i yeye kollektsiya. [Disturbances in the balance of microflora and its collection]. Effektivnaya farmakoterapiya. 2013; 41: 16–20. (In Russian).
10. Lawley T.D., Walker A.W. Intestinal colonization resistance. Immunology. 2013; 38(1): 1–11. DOI: 10.1111/j.1365-2567.2012.03616.x.
11. Lammers K.M., Brigidi P., Gionchetti B.V.P. et al. Immunomodulatory effects of probiotic bacteria DNA: IL-1 and IL-10 response in human peripheral blood mononuclear cells. FEMS Immunology & Medical Microbiology. 2003; 38(2): 165–72. DOI: 10.1016/S0928-8244(03)00144-5.
12. Eckburg P.B., Bik E.M,. Bernstein C.N. et al. Diversity of the Human Intestinal Microbial Flora. Science. 2005; 308(5728): 1635–8. DOI: 10.1126/science.1110591.
13. Nikolayeva I.V., Tsaregorodtsev A.D., Shaykhiyeva G.S. Formirovaniye kishechnoy mikrobioty rebenka i faktory, vliyayushchiye na etot protsess. [Formation of the child's intestinal microbiota and factors influencing this process]. Ros. vestn. perinatol. i pediatr. 2018; 63(3): 13–8. DOI: 10.21508/1027-4065-2018-63-3-13-18. (In Russian).
14. Mariat D., Firmesse O., Levenez F. et al. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiology. 2009; 9: 123. DOI: 10.1186/1471-2180-9-123.
15. Dieterich W., Schink M., Zopf Y. Microbiota in the Gastrointestinal Tract. Med Sci (Basel). 2018; 6(4): 116. DOI: 10.3390/medsci6040116.
16. Pereira F.C., Berry D. Microbial nutrient niches in the gut. Environ Microbiol. 2017; 19(4): 1366–78. DOI: 10.1111/1462-2920.13659.
17. Liou C.W., Yao T.H., Wu W.L. Intracerebroventricular Delivery of Gut-Derived Microbial Metabolites in Freely Moving Mice. J. Vis. Exp. 2022; 184: e63972. DOI: 10.3791/63972.
18. Koh A., de Vadder F., Kovatcheva-Datchary P., Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2016; 165: 1332–45. DOI: 10.1016/j.cell.2016.05.041.
19. Hopkins M.J., Macfarlane G.T. Nondigestible oligosaccharides enhance bacterial colonization resistance against Clostridium difficile in vitro. 2003; 69(4): 1920–7. DOI: 10.1128/AEM.69.4.1920-1927.2003.
20. McKenney P.T., Pamer E.G. From hype to hope: the gut microbiota in enteric infectious disease. Cell. 2015; 163(6): 1326–32. DOI: 10.1016/j.cell.2015.11.032.
21. Bin P., Tang Z., Liu S. Intestinal microbiota mediates Enterotoxigenic Escherichia coli-induced diarrhea in piglets. BMC Vet Res. 2018; 14(385). DOI: 10.1186/s12917-018-1704-9.
22. Zhang Y., Tan P., Zhao Y., Ma X. Enterotoxigenic Escherichia coli: intestinal pathogenesis mechanisms and colonization resistance by gut microbiota. Gut Microbes. 2022; 14(1): 2055943. DOI: 10.1080/19490976.2022.2055943.
23. Pace F., Rudolph S.E., Chen Y. et al. The Short-Chain Fatty Acids Propionate and Butyrate Augment Adherent-Invasive Escherichia coli Virulence but Repress Inflammation in a Human Intestinal Enteroid Model of Infection. 2021; 9(2): e0136921. DOI: 10.1128/Spectrum.01369-21.

24. Bondarenko V.M., Likhoded V.G., Fialkina S.V. Kommensal'naya mikroflora i endogennyye induktory patofiziologicheskikh reaktsiy vrozhdennogo immuniteta. [Commensal microflora and endogenous inducers of pathophysiological reactions of innate immunity]. Zhurnal mikrobiologii, epidemiologii, immunobiologii. 2015; 1: 81–5. (In Russian).
25. Soltani S., Hammami R., Cotter P.D. et al. Bacteriocins as a new generation of antimicrobials: toxicity aspects and regulations. FEMS Microbiol. Rev. 2021; 45: 1–24. DOI: 10.1093/femsre/fuaa039.
26. Donia S.M., Cimermancic P., Schulze C.J. et al. A systematic analysis of biosynthetic gene clusters in the human microbiome reveals a common family of antibiotics. Cell. 2014; 158(6): 1402–14. DOI: 10.1016/j.cell.2014.08.032.
27. Hanchi H., Hammami R., Gingras H. et al. Inhibition of MRSA and of Clostridium difficile by durancin 61A: synergy with bacteriocins and antibiotics. Future Microbiol. 2017; 12: 205–12. DOI: 10.2217/fmb-2016-0113.
28. Kumarasamy K., Toleman M.A., Walsh T.R. et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. The Lancet Infectious Diseases. 2010; 10(9): 597–602. DOI: 10.1016/S1473-3099(10)70143-2.
29. Yu H., Li N., Zeng X. et al. A comprehensive antimicrobial activity evaluation of the recombinant microcin J25 against the foodborne pathogens Salmonella and E. coli O157:H7 by using a matrix of conditions. Front Microbiol. 2019; 10: 1954. DOI: 10.3389/fmicb.2019.01954.
30. Gomaa A.I., Martinent C., Hammami R. et al. Dual coating of liposomes as encapsulating matrix of antimicrobial peptides: development and characterization. Front Chem. 2017; 5: 103. DOI: 10.3389/fchem.2017.00103.
31. Dreyer L., Smith C., Deane S.M. et al. Migration of bacteriocins across gastrointestinal epithelial and vascular endothelial cells, as determined using in vitro simulations. Sci Rep 2019; 9: 1–11. DOI: 10.1038/s41598-019-47843-9.
32. McCaughey L.C., Ritchie N.D., Douce G.R. et al. Efficacy of species-specific protein antibiotics in a murine model of acute Pseudomonas aeruginosa lung infection. Sci Rep. 2016; 6: 30201. DOI: 10.1038/srep30201.
33. Osakowicz C., Fletcher L., Caswell J.L., Li J. Protective and Anti-Inflammatory Effects of Protegrin-1 on Citrobacter rodentium Intestinal Infection in Mice. Int J Mol Sci. 2021; 22(17): 9494. DOI: 10.3390/ijms22179494.
34. McGuckin M.A., Linden S.K., Sutton P., Florin T.H. Mucin dynamics and enteric pathogens. Nat Rev Microbiol. 2011; 9: 265e78. DOI: 10.1038/nrmicro2538.
35. Akin'shina A.I., Smirnova D.V., Zagaynova A.V. i dr. Perspektivy ispol'zovaniya metodov korrektsii mikrobioty pri terapii vospalitel'nykh zabolevaniy kishechnika. [Prospects for using microbiota correction methods in the treatment of inflammatory bowel diseases]. Rossiyskiy zhurnal gastroenterologii, gepatologii, koloproktologii. 2019; 29(2): 12–22. DOI: 10.22416/1382-4376-2019-29-2-12-22. (In Russian).
36. De Sá Almeida J.S., de Oliveira Marre A.T., Teixeira F.L. et al. Lactoferrin and lactoferricin B reduce adhesion and biofilm formation in the intestinal symbionts Bacteroides fragilis and Bacteroides thetaiotaomicron. Anaerobe. 2020; 64: 102232. DOI: 10.1016/j.anaerobe.2020.102232.
37. Caruso G., Giammanco A., Cardamone C. et al. Extra-Intestinal Fluoroquinolone-Resistant Escherichia coli Strains Isolated from Meat. Biomed Res Int. 2018: 8714975. DOI: 10.1155/2018/8714975.
38. Johnson J.R., Russo T.A. Extraintestinal pathogenic Escherichia coli: "The other bad E. coli". The Journal of Laboratory and Clinical Medicine. 2002; 139(3): 155–62.
39. McKenney P.T., Pamer E.G. From hype to hope: The gut microbiota in enteric infectious disease. Cell. 2015; 163(6): 1326–36. DOI: 10.1016/j.cell.2015.11.032.
40. Mustayeva G.B. Osobennosti techeniya klebsiyelleznoy infektsii po dannym Samarkandskoy oblastnoy klinicheskoy bol'nitsy. [Features of the course of Klebsiella infection according to the Samarkand Regional Clinical Hospital]. Vestnik nauki i obrazovaniya. 2020; 18-2 (96): 81–5. (In Russian).
41. Li B., Zhang J., Chen Y. et al. Alterations in microbiota and their metabolites are associated with beneficial effects of bile acid sequestrant on icteric primary biliary Cholangitis. Gut Microbes. 2021; 13(1): e1946366.
42. Tang R., Wei Y., Li Y. et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut. 2018; 67: 534–71.
43. Khayertynov KH.S., Anokhin V.A., Rizvanov A.A. i dr. Virulentnost' i antibiotikorezistentnost' izolyatov Klebsiella pneumoniae u novorozhdennykh s lokalizovannymi i generalizovannymi formami klebsiyelleznoy infektsii. [Virulence and antibiotic resistance of Klebsiella pneumoniae isolates in newborns with localized and generalized forms of

Klebsiella infection]. Rossiyskiy vestnik perinatal'noy patologii i pediatrii. 2018; 63(5): 139–46. (In Russian).
44. Bor M., Ilhan O. Carbapenem-Resistant Klebsiella pneumoniae Outbreak in a Neonatal Intensive Care Unit: Risk Factors for Mortality. Journal of Tropical Pediatrics. 2021; 67(3): fmaa057. DOI: 10.1093/tropej/fmaa057.
45. Koroleva I.V., Gonchar N.V., Berezina L.V., Suvorov A.N. Mikrobiologicheskiy i molekulyarno-geneticheskiy analiz faktorov patogennosti K. pneumoniae, vyzyvayushchikh ostryye kishechnyye infektsii u detey grudnogo vozrasta. [Microbiological and molecular genetic analysis of pathogenicity factors of K. pneumoniae causing acute intestinal infections in infants]. Vestnik Rossiyskoy Voyenno-meditsinskoy akademii. 2008; 1(21): 107–13. (In Russian).
46. De Sales R., Leaden L., Migliorini L.B., Severino P.A Comprehensive Genomic Analysis of the Emergent Klebsiella pneumoniae ST16 Lineage: Virulence, Antimicrobial Resistance and a Comparison with the Clinically Relevant ST11 Strain. Pathogens. 2022; 11(12): 394. DOI: 10.3390/pathogens11121394.
47. Bengoechea J.A., Sa Pessoa J. Klebsiella pneumoniae Infection Biology: Living to Counteract Host Defences. FEMS Microbiology Review. 2019; 43(2): 123–44. DOI: 10.1093/femsre/fuy043.
48. Broberg C.A., Palacios M., Miller V.L. Klebsiella: a long way to go towards understanding this enigmatic jet-setter. F1000Prime Rep. 2014; 6: 64. DOI: 10.12703/P6-64. eCollection 2014.
49. Savilov Ye.D., Anganova Ye.V., Dukhanina A.V., Chemezova N.N. Fenotipicheskiye markery patogennosti u predstaviteley semeystva Enterobacteriaceae, vydelennykh ot detey pri ostrykh kishechnykh infektsiyakh. [Phenotypic markers of pathogenicity in representatives of the Enterobacteriaceae family isolated from children with acute intestinal infections]. Sibirskiy meditsinskiy zhurnal (Irkutsk). 2012; 113(6): 93–5. (In Russian).
50. Gonchar N.V., Kopersak A.K., Skripchenko N.V. i dr. Rezistentnost' k antibakterial'nym preparatam i bakteriofagam izolyatov Klebsiella pneumoniae, vydelennykh ot detey raznogo vozrasta s kishechnymi infektsiyami. [Resistance to antibacterial drugs and bacteriophages of Klebsiella pneumoniae isolates isolated from children of different ages with intestinal infections]. Detskiye infektsii. 2023; 22(1): 27–31. DOI: 10.22627/2072-8107-2023-22-1-27-31. (In Russian).
51. Qiu Y., Lin D., Xu Y. et al. Invasive Klebsiella pneumoniae Infections in Community — Settings and Healthcare Settings. Infect Drug Resist. 2021; 14: 2647–56.
52. Rakotondrasoa A., Passet V., Herindrainy P. et al. Characterization of Klebsiella pneumoniae isolates from a mother-child cohort in Madagascar. J Antimicrob Chemother. 2020; 75(7): 1736–46. DOI: 10.1093/jac/dkaa107.
53. Semenova D.R., Nikolayeva I.V., Fialkina S.V. i dr. Chastota kolonizatsii «gipervirulentnymi» shtammami Klebsiella pneumoniae novorozhdennykh i grudnykh detey s vnebol'nichnoy i nozokomial'noy klebsiyelloznoy infektsiyey. [Frequency of colonization with "hypervirulent" strains of Klebsiella pneumoniae in newborns and infants with community-acquired and nosocomial Klebsiella infection]. Rossiyskiy vestnik perinatologii i pediatrii. 2020; 65(5): 158–63. DOI: 10.21508/1027-4065-2020-65-5-158-163. (In Russian).
54. Kharchenko G.A., Kimirilova O.G. Kliniko-epidemiologicheskiye osobennosti ostrykh kishechnykh infektsiy, vyzvannykh uslovno-patogennymi enterobakteriyami u detey rannego vozrasta. [Clinical and epidemiological features of acute intestinal infections caused by opportunistic enterobacteria in young children]. Lechashchiy Vrach. 2021; 4(24): 37–41. DOI: 10.51793/OS.2021.62.72.007. (In Russian).
55. Tkhakushinova N.Kh., Gorelov A.V. Povtornyye ostryye kishechnyye infektsii rotavirusnoy etiologii u detey: osobennosti techeniya, faktory riska, usloviya razvitiya i iskhody. [Repeated acute intestinal infections of rotavirus etiology in children: clinical features, risk factors, development conditions and outcomes]. Infektsionnyye bolezni. 2017; 15(1): 29–34. DOI: 10.20953/1729-9225-2017-1-29-34. (In Russian).
56. Rodríguez-Díaz J., García-Mantrana I., Vila-Vicent S. et al. Relevance of secretor status genotype and microbiota composition in susceptibility to rotavirus and norovirus infections in humans. Sci Rep. 2017; 7: 45559. DOI: 10.1038/srep45559.
57. Azagra-Boronat I., Massot-Cladera M., Knipping K. et al. Oligosaccharides Modulate Rotavirus-Associated Dysbiosis and TLR Gene Expression in Neonatal Rats. Cells. 2019; 8: 876. DOI: 10.3390/cells8080876.
58. Mizutani T., Aboagye S.Y., Ishizaka A. et al. Gut microbiota signature of pathogen-dependent dysbiosis in viral gastroenteritis. Sci Rep. 2021; 11(1): 13945. DOI: 10.1038/s41598-021-93345-y.
59. Wu P., Sun P., Nie K. et al. A Gut Commensal Bacterium Promotes Mosquito Permissiveness to Arboviruses. Cell Host & Microbe. 2019; 25(1): 101–12. DOI: 10.1016/j.chom.2018.11.004.
60. Chicherin I.Yu., Pogorel'skiy I.P., Kolodkin A.M. i dr. Rol' kolonizatsionnoy rezistentnosti slizistoy obo-

lochki zheludka i kishechnika v razvitii infektsiy bakterial'noy prirody zheludochno-kishechnogo trakta. [he role of colonization resistance of the mucous membrane of the stomach and intestines in the development of bacterial infections of the gastrointestinal tract] Infektsionnyye bolezni. 2019; 17(3): 55–68. DOI: 10.20953/1729-9225-2019-3-55-68. (In Russian).

ЛИТЕРАТУРА

1. О состоянии санитарно-эпидемиологического благополучия населения в Российской Федерации в 2022 году: Государственный доклад. М.: Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека. 2023.
2. Сергевнин В.И. Современные тенденции в многолетней динамике заболеваемости острыми кишечными инфекциями бактериальной и вирусной этиологии. Эпидемиология и вакцинопрофилактика. 2020; 19(4): 14–9.
3. Карпович Г.С., Васюнин А.В., Краснова Е.И., Дегтярев А.И. Эпидемиологические и лабораторные особенности кишечных инфекций вирусной этиологии у детей первого года жизни в Новосибирске. Сибирский медицинский вестник. 2020; 2: 35–40.
4. Ковалев О.Б., Молочкова О.В., Коняев К.С. и др. Этиология и клинические проявления острых кишечных инфекций у детей, по данным стационара за 2016–2018 гг. Детские инфекции. 2019; 18(2): 54–7.
5. Мурзабаева Р.Т., Мавзютов А.Р., Валишин Д.А. Клинико-иммунологические параллели при острых кишечных инфекциях, вызванных условно-патогенными энтеробактериями. Инфекционные болезни. 2018; 16(4): 79–85.
6. Гончар Н.В., Ермоленко К.Д., Климова О.И. и др. Бактериальные кишечные инфекции с синдромом гемоколита у детей: этиология, лабораторная диагностика. Медицина экстремальных ситуаций. 2019; 1: 90–104.
7. Бондаренко В.М., Рыбальченко О.В. Оценка микробиоты и пробиотических штаммов с позиций новых научных технологий. Фарматека. 2016; 11(324): 21–33.
8. Murphy C., Clegg S. Klebsiella pneumoniae and type 3 fimbriae: nosocomial infection, regulation and biofilm formation. Future Microbiol. 2012; 7 (8): 991–1002. DOI: 10.2217/fmb.12.74.
9. Минушкин О.Н., Елизаветина Г.А., Ардатская М.Д. Нарушения баланса микрофлоры и ее коллекция. Эффективная фармакотерапия. 2013; 41: 16–20.
10. Lawley T.D., Walker A.W. Intestinal colonization resistance. Immunology. 2013; 38(1): 1–11. DOI: 10.1111/j.1365-2567.2012.03616.x.
11. Lammers K.M., Brigidi P., Gionchetti B.V.P. et al. Immunomodulatory effects of probiotic bacteria DNA: IL-1 and IL-10 response in human peripheral blood mononuclear cells. FEMS Immunology & Medical Microbiology. 2003; 38(2): 165–72. DOI: 10.1016/S0928-8244(03)00144-5.
12. Eckburg P.B., Bik E.M,. Bernstein C.N. et al. Diversity of the Human Intestinal Microbial Flora. Science. 2005; 308(5728): 1635–8. DOI: 10.1126/science.1110591.
13. Николаева И.В., Царегородцев А.Д., Шайхиева Г.С. Формирование кишечной микробиоты ребенка и факторы, влияющие на этот процесс. Рос. вестн. перинатол. и педиатр 2018; 63(3): 13–8. DOI: 10.21508/1027-4065-2018-63-3-13-18.
14. Mariat D., Firmesse O., Levenez F. et al. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiology. 2009; 9: 123. DOI: 10.1186/1471-2180-9-123.
15. Dieterich W., Schink M., Zopf Y. Microbiota in the Gastrointestinal Tract. Med Sci (Basel). 2018; 6(4): 116. DOI: 10.3390/medsci6040116.
16. Pereira F.C., Berry D. Microbial nutrient niches in the gut. Environ Microbiol. 2017; 19(4): 1366–78. DOI: 10.1111/1462-2920.13659.
17. Liou C.W., Yao T.H., Wu W.L. Intracerebroventricular Delivery of Gut-Derived Microbial Metabolites in Freely Moving Mice. J. Vis. Exp. 2022; 184: e63972. DOI: 10.3791/63972.
18. Koh A., de Vadder F., Kovatcheva-Datchary P., Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2016; 165: 1332–45. DOI: 10.1016/j.cell.2016.05.041.
19. Hopkins M.J., Macfarlane G.T. Nondigestible oligosaccharides enhance bacterial colonization resistance against Clostridium difficile in vitro. 2003; 69(4): 1920–7. DOI: 10.1128/AEM.69.4.1920-1927.2003.
20. McKenney P.T., Pamer E.G. From hype to hope: the gut microbiota in enteric infectious disease. Cell. 2015; 163(6): 1326–32. DOI: 10.1016/j.cell.2015.11.032.
21. Bin P., Tang Z., Liu S. Intestinal microbiota mediates Enterotoxigenic Escherichia coli-induced diarrhea in piglets. BMC Vet Res. 2018; 14(385). DOI: 10.1186/s12917-018-1704-9.
22. Zhang Y., Tan P., Zhao Y., Ma X. Enterotoxigenic Escherichia coli: intestinal pathogenesis mechanisms and colonization resistance by gut microbiota. Gut Microbes. 2022; 14(1): 2055943. DOI: 10.1080/19490976.2022.2055943.
23. Pace F., Rudolph S.E., Chen Y. et al. The Short-Chain Fatty Acids Propionate and Butyrate Aug-

ment Adherent-Invasive Escherichia coli Virulence but Repress Inflammation in a Human Intestinal Enteroid Model of Infection. 2021; 9(2): e0136921. DOI: 10.1128/Spectrum.01369-21.
24. Бондаренко В.М., Лиходед В.Г., Фиалкина С.В. Комменсальная микрофлора и эндогенные индукторы патофизиологических реакций врожденного иммунитета. Журнал микробиологии, эпидемиологии, иммунобиологии. 2015; 1: 81–5.
25. Soltani S., Hammami R., Cotter P.D. et al. Bacteriocins as a new generation of antimicrobials: toxicity aspects and regulations. FEMS Microbiol. Rev. 2021; 45: 1–24. DOI: 10.1093/femsre/fuaa039.
26. Donia S.M., Cimermancic P., Schulze C.J. et al. A systematic analysis of biosynthetic gene clusters in the human microbiome reveals a common family of antibiotics. Cell. 2014; 158(6): 1402–14. DOI: 10.1016/j.cell.2014.08.032.
27. Hanchi H., Hammami R., Gingras H. et al. Inhibition of MRSA and of Clostridium difficile by durancin 61A: synergy with bacteriocins and antibiotics. Future Microbiol. 2017; 12: 205–12. DOI: 10.2217/fmb-2016-0113.
28. Kumarasamy K., Toleman M.A., Walsh T.R. et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. The Lancet Infectious Diseases. 2010; 10(9): 597–602. DOI: 10.1016/S1473-3099(10)70143-2.
29. Yu H., Li N., Zeng X. et al. A comprehensive antimicrobial activity evaluation of the recombinant microcin J25 against the foodborne pathogens Salmonella and E. coli O157:H7 by using a matrix of conditions. Front Microbiol. 2019; 10: 1954. DOI: 10.3389/fmicb.2019.01954.
30. Gomaa A.I., Martinent C., Hammami R. et al. Dual coating of liposomes as encapsulating matrix of antimicrobial peptides: development and characterization. Front Chem. 2017; 5: 103. DOI: 10.3389/fchem.2017.00103.
31. Dreyer L., Smith C., Deane S.M. et al. Migration of bacteriocins across gastrointestinal epithelial and vascular endothelial cells, as determined using in vitro simulations. Sci Rep 2019; 9: 1–11. DOI: 10.1038/s41598-019-47843-9.
32. McCaughey L.C., Ritchie N.D., Douce G.R. et al. Efficacy of species-specific protein antibiotics in a murine model of acute Pseudomonas aeruginosa lung infection. Sci Rep. 2016; 6: 30201. DOI: 10.1038/srep30201.
33. Osakowicz C., Fletcher L., Caswell J.L., Li J. Protective and Anti-Inflammatory Effects of Protegrin-1 on Citrobacter rodentium Intestinal Infection in Mice. Int J Mol Sci. 2021; 22(17): 9494. DOI: 10.3390/ijms22179494.
34. McGuckin M.A., Linden S.K., Sutton P., Florin T.H. Mucin dynamics and enteric pathogens. Nat Rev Microbiol. 2011; 9: 265e78. DOI: 10.1038/nrmicro2538.
35. Акиньшина А.И., Смирнова Д.В., Загайнова А.В. и др. Перспективы использования методов коррекции микробиоты при терапии воспалительных заболеваний кишечника. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2019; 29(2): 12–22. DOI: 10.22416/1382-4376-2019-29-2-12-22.
36. De Sá Almeida J.S., de Oliveira Marre A.T., Teixeira F.L. et al. Lactoferrin and lactoferricin B reduce adhesion and biofilm formation in the intestinal symbionts Bacteroides fragilis and Bacteroides thetaiotaomicron. Anaerobe. 2020; 64: 102232. DOI: 10.1016/j.anaerobe.2020.102232.
37. Caruso G., Giammanco A., Cardamone C. et al. Extra-Intestinal Fluoroquinolone-Resistant Escherichia coli Strains Isolated from Meat. Biomed Res Int. 2018: 8714975. DOI: 10.1155/2018/8714975.
38. Johnson J.R., Russo T.A. Extraintestinal pathogenic Escherichia coli: "The other bad E. coli". The Journal of Laboratory and Clinical Medicine. 2002; 139(3): 155–62.
39. McKenney P.T., Pamer E.G. From hype to hope: The gut microbiota in enteric infectious disease. Cell. 2015; 163(6): 1326–36. DOI: 10.1016/j.cell.2015.11.032.
40. Мустаева Г.Б. Особенности течения клебсиеллезной инфекции по данным Самаркандской областной клинической больницы. Вестник науки и образования. 2020; 18-2 (96): 81–5.
41. Li B., Zhang J., Chen Y. et al. Alterations in microbiota and their metabolites are associated with beneficial effects of bile acid sequestrant on icteric primary biliary Cholangitis. Gut Microbes. 2021; 13(1): e1946366.
42. Tang R., Wei Y., Li Y. et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut. 2018; 67: 534–71.
43. Хаертынов Х.С., Анохин В.А., Ризванов А.А. и др. Вирулентность и антибиотикорезистентность изолятов Klebsiella pneumoniae у новорожденных с локализованными и генерализованными формами клебсиеллезной инфекции. Российский вестник перинатальной патологии и педиатрии. 2018; 63(5): 139–46.
44. Bor M., Ilhan O. Carbapenem-Resistant Klebsiella pneumoniae Outbreak in a Neonatal Intensive Care Unit: Risk Factors for Mortality. Journal

of Tropical Pediatrics. 2021; 67(3): fmaa057. DOI: 10.1093/tropej/fmaa057.
45. Королева И.В., Гончар Н.В., Березина Л.В., Суворов А.Н. Микробиологический и молекулярно-генетический анализ факторов патогенности K. pneumoniae, вызывающих острые кишечные инфекции у детей грудного возраста. Вестник Российской Военно-медицинской академии. 2008; 1(21): 107–13.
46. De Sales R., Leaden L., Migliorini L.B., Severino P. A Comprehensive Genomic Analysis of the Emergent Klebsiella pneumoniae ST16 Lineage: Virulence, Antimicrobial Resistance and a Comparison with the Clinically Relevant ST11 Strain. Pathogens. 2022; 11(12): 394. DOI: 10.3390/pathogens11121394.
47. Bengoechea J.A., Sa Pessoa J. Klebsiella pneumoniae Infection Biology: Living to Counteract Host Defences. FEMS Microbiology Review. 2019; 43(2): 123–44. DOI: 10.1093/femsre/fuy043.
48. Broberg C.A., Palacios M., Miller V.L. Klebsiella: a long way to go towards understanding this enigmatic jet-setter. F1000Prime Rep. 2014; 6: 64. DOI: 10.12703/P6-64. eCollection 2014.
49. Савилов Е.Д., Анганова Е.В., Духанина А.В., Чемезова Н.Н. Фенотипические маркеры патогенности у представителей семейства Enterobacteriaceae, выделенных от детей при острых кишечных инфекциях. Сибирский медицинский журнал (Иркутск). 2012; 113(6): 93–5.
50. Гончар Н.В., Коперсак А.К., Скрипченко Н.В. и др. Резистентность к антибактериальным препаратам и бактериофагам изолятов Klebsiella pneumoniae, выделенных от детей разного возраста с кишечными инфекциями. Детские инфекции. 2023; 22(1): 27–31. DOI: 10.22627/2072-8107-2023-22-1-27-31.
51. Qiu Y., Lin D., Xu Y. et al. Invasive Klebsiella pneumoniae Infections in Community–Settings and Healthcare Settings. Infect Drug Resist. 2021; 14: 2647–56.
52. Rakotondrasoa A., Passet V., Herindrainy P. et al. Characterization of Klebsiella pneumoniae isolates from a mother-child cohort in Madagascar. J Antimicrob Chemother. 2020; 75(7): 1736–46. DOI: 10.1093/jac/dkaa107.
53. Семенова Д.Р., Николаева И.В., Фиалкина С.В. и др. Частота колонизации «гипервирулентными» штаммами Klebsiella pneumoniae новорожденных и грудных детей с внебольничной и нозокомиальной клебсиеллёзной инфекцией. Российский вестник перинатологии и педиатрии. 2020; 65(5): 158–63. DOI: 10.21508/1027-4065-2020-65-5-158-163.
54. Харченко Г.А., Кимирилова О.Г. Клинико-эпидемиологические особенности острых кишечных инфекций, вызванных условно-патогенными энтеробактериями у детей раннего возраста. Лечащий Врач. 2021; 4(24): 37–41. DOI: 10.51793/OS.2021.62.72.007.
55. Тхакушинова Н.Х., Горелов А.В. Повторные острые кишечные инфекции ротавирусной этиологии у детей: особенности течения, факторы риска, условия развития и исходы. Инфекционные болезни. 2017; 15(1): 29–34. DOI: 10.20953/1729-9225-2017-1-29-34.
56. Rodríguez-Díaz J., García-Mantrana I., Vila-Vicent S. et al. Relevance of secretor status genotype and microbiota composition in susceptibility to rotavirus and norovirus infections in humans. Sci Rep. 2017; 7: 45559. DOI: 10.1038/srep45559.
57. Azagra-Boronat I., Massot-Cladera M., Knipping K. et al. Oligosaccharides Modulate Rotavirus-Associated Dysbiosis and TLR Gene Expression in Neonatal Rats. Cells. 2019; 8: 876. DOI: 10.3390/cells8080876.
58. Mizutani T., Aboagye S.Y., Ishizaka A. et al. Gut microbiota signature of pathogen-dependent dysbiosis in viral gastroenteritis. Sci Rep. 2021; 11(1): 13945. DOI: 10.1038/s41598-021-93345-y.
59. Wu P., Sun P., Nie K. et al. A Gut Commensal Bacterium Promotes Mosquito Permissiveness to Arboviruses. Cell Host & Microbe. 2019; 25(1): 101–12. DOI: 10.1016/j.chom.2018.11.004.
60. Чичерин И.Ю., Погорельский И.П., Колодкин А.М. и др. Роль колонизационной резистентности слизистой оболочки желудка и кишечника в развитии инфекций бактериальной природы желудочно-кишечного тракта. Инфекционные болезни. 2019; 17(3): 55–68. DOI: 10.20953/1729-9225-2019-3-55-68.

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THE ROLE OF HOMOCYSTEIN IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION IN OBESITY AND COMORBID DISEASES

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Abstract. Homocysteine (Hc) is an amino acid that is involved in the pathogenesis of arterial hypertension (AH) by inducing prothrombotic and pro-inflammatory effects, by increasing oxidative stress, endothelial dysfunction and smooth muscle cell proliferation. However, its role in the development of hypertension with comorbid pathologies, such as obesity and related metabolic disorders, has not been studied enough.

Key words: *homocysteine; obesity; metabolic syndrome; insulin resistance.*

РОЛЬ ГОМОЦИСТЕИНА В ПАТОГЕНЕЗЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ ПРИ ОЖИРЕНИИ И КОМОРБИДНЫХ ЗАБОЛЕВАНИЯХ

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Резюме. Гомоцистеин (Гц) — это аминокислота, которая принимает участие в патогенезе артериальной гипертензии (АГ) путем индукции протромботических и провоспалительных эффектов, путем увеличения окислительного стресса, эндотелиальной дисфункции и пролиферации клеток гладких мышц. Однако его роль в развитии АГ при коморбидных патологиях, например при ожирении и связанных с ним нарушениях обменных процессов, изучена недостаточно.

Ключевые слова: *гомоцистеин; ожирение; метаболический синдром; инсулинорезистентность.*

INTRODUCTION

By the end of the XX century, a cluster of major risk factors for cardiovascular disease (CVD) has been described, which includes simultaneous presence of obesity, type 2 diabetes mellitus (T2DM), hyperlipidaemia and arterial hypertension (AH). This simultaneous occurrence of risk factors led researchers to assume the existence of a peculiar pathophysiological state, later described as "metabolic syndrome", which emphasize the presence of pathogenetic links between these conditions. However, at the moment some researchers differentiate abdominal obesity as a separate independent risk factor for the development of atherosclerosis, coronary heart disease (CHD) and hypertension (HT) [1, 2].

According to the data published in recent years, hyperhomocysteinaemia plays an important role

in the development of metabolic syndrome (MS) [3]. High homocysteine levels are associated with cardiovascular risk, risk of insulin resistance syndromes (IR), presence of nonalcoholic fatty liver disease (NAFLD) and many other diseases [4–6]. However, the relationship between abdominal obesity (as one of the main elements of MS) and hyperhomocysteinaemia has been insufficiently studied by the moment. Taking into account the prevalence of these conditions and their proven impact on the development and progression of cardiovascular pathology, the study of this problem has a great scientific and practical interest [7].

OBJECTIVE

The aim of this review is to present and analyze the current data concerning the role of homocysteine in the pathogenesis of arterial hypertension in obesity and related comorbid conditions.

MATERIALS AND METHODS

To reach this objective, scientific publications in Russian and English have been analuzed for the period from 2016 to 2022, the publications were indexed in RINC, PubMed, MEDLINE, and Cochrane Library databases. In isolated cases, earlier publications were used due to their priority or historical value.

HOMOCYSTEINE, ITS METABOLISM, NORMS AND CAUSES OF ELEVATION

In 1932, chemists Butz and Vigneaud described a previously unknown amino acid synthesized by exposing high concentration of sulfuric acid to metionine. The obtained compound differed from cysteine by one carbon atom and was therefore named "homocysteine". Homo (from Greek ομος) is a component of compound words meaning "similar" [8, 9].

Homocysteine (Hcy) is an intermediate metabolite in the folate cycle containing thiol groups, which is produced in all cells through transmethylation reactions of dietary methionine [10, 11].

The level of Hcy in human blood depends on age, sex, nutritional quality and genetic characteristics. During life, the level of Hcy in blood gradually increases. In children before puberty, the levels of Hz in boys and girls are approximately the same (about 5 μmol/L). During puberty, Hcy levels rise to 6–7 μmol/L, and this increase is more pronounced in boys than in girls. In adults, the balance is also maintained, and Hcy levels in males are usually higher than in females, which is attributed to greater muscle mass. Hcy levels gradually increase with age, women have a higher rate of increase than men. The gradual increase in Hcy levels connected with age has been attributed to a decline in the renal function [9, 12].

Homocysteine is metabolized by two pathways: by the transfer of the sulfate group in the presence of vitamin B6, or by remethylation in the presence of vitamin B12 and folic acid. Approximately 5–10% of the total daily cellular production of Hcy, which is not metabolized within the cell, passes into the blood plasma, where about 80% is in the albumin-bound state and about 1% is in the free form. The remaining part is presented as disulfides with cysteine, homocysteine (homocystine), and other compounds. All homocysteine-containing derivatives are defined as "total plasma homocysteine" [11, 12].

Normal levels of Hcy range from 5 to 15 μmol/L, and this baseline is maintained in healthy individuals due to constant renal clearance[11]. According to other sources, normal rates of Hcy ranges from 10–11 μmol/L. Homocysteine concentration in blood plasma within 15–30 μmol/L indicates moderate hyperhomocysteinaemia, from 30 to 100 μmol/L — intermediate, and more than 100 μmol/L — severe [9].

The main causes of hyperhomocysteinaemia (HHcy is a condition characterized by elevated levels of Hcy in the blood) can be divided into hereditary (genetic) and non-hereditary (acquired). Thus, genetic factors are gene mutations that encode the synthesis of an enzyme involved in the processes of homocysteine formation. The most studied is a defect in the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyl-tetrahydrofolate. The latter is the major circulating form of folic acid, high concentrations of which are required for the conversion of excess homocysteine to methionine by the methionine-synthase enzyme. Thus, a decrease in the activity of the MTHFR enzyme caused by single nucleotide polymorphisms contributes to the accumulation of homocysteine [13].

Non-genetic factors of HHcy include autoimmune processes, consumption of large amounts of methionine-rich foods, large amounts of caffeine, smoking, alcohol consumption, sedentary lifestyle, vitamin deficiency states (especially deficiencies of B_1, B_6, B_{12}, folic acid), and kidney diseases [8]. Elevated Hcy levels are also observed in people who take certain medications, such

as methotrexate, cholestyramine, niacin, and a number of antiepileptic drugs, all of which affect folic acid metabolism. Drugs that affect vitamin B_{12} absorption (e.g., было выделено H_2-receptor antagonists) or drugs that inhibit vitamin B_6 activity (e.g., euphylline) may also increase Hz in the blood [9].

Although the description of Hcy and studies on the role of this amino acid began more than 90 years ago, the most active study concerning Hcy significance has taken place in recent decades [14]. Thus, nowadays there is a large number of publications regarding the association of hyperhomocysteinaemia with various pathologies: CVDs, neuropsychiatric disorders (autism spectrum disorders, migraines, etc.), neurodegenerative, allergic, oncological and autoimmune diseases, vasculitis, end-stage kidney disease, osteoporosis, undifferentiated connective tissue dysplasia, various lesions of the reproductive system (pregnancy abnormalities, polycystic ovary syndrome — PCOS) and others. [3, 8, 9, 14, 15].

A correlation between HHcy and obesity is seen in the structure of many studies, but the data remain contradictory. In 2020, Jinxiang Wang and Dingyun You conducted a meta-analysis based on 14 publications selected using NOS and AHRQ to evaluate the relationship between blood homocysteine concentration and obesity. The meta-analysis showed significantly lower homocysteine concentrations in the control group than in obese patients, regardless of nutritional status, dietary habits, insulin resistance (IR) status, special disease history, history of medications taken, genetic background, etc. Homocysteine concentration was higher in patients with obesity and PCOS than in PCOS patients without obesity, suggesting that obesity increases the concentration of Hcy in the blood even if there are conditions that already include an increase in this laboratory parameter [16].

The role of HHcy in pathogenesis of comorbid diseases (atherosclerosis, Hypertention, IR, T2DM, NAFLD, etc.) is well studied , while its place in the direct development of obesity remains controversial. However, the analysis of literature make it possible to indicate common links between the pathogenesis and HHcy, which will be discussed below.

INFLAMMATION IN ADIPOSE TISSUE AND THE ROLE OF HOMOCYSTEINE

According to numerous studies, it has been proved that obesity leads to subclinical systemic inflammation, which influence on forming vicious circles in the pathogenesis of this disease and related comorbid conditions (cardiovascular diseases, type 2 diabetes mellitus, uric acid metabolism disorder, sex hormone imbalance, non-alcoholic fatty liver disease, oncologic diseases) [17, 18].

Inflammation of adipose tissue begins with the recruitment of monocytes and their extravasation from blood vessels into adipose tissue, where they acquire the status of macrophages. Chemokines, among others, are responsible for the processes of their adhesion and migration. Chemokines are produced in huge quantities by hypertrophied adipocytes in adipose tissue. One of the most known and active variants of chemokines is MCP-1 (monocyte chemoattractant protein 1), which stimulates the migration of monocytes into the vessel intima [17]. The study of G. Wang and Y.L. Siow proved that the increased expression of MCP-1 was associated with increased concentrations of homocysteine [19]. Thus, it can be assumed that hyperhomocysteinaemia aggravates extravasation of monocytes and further infiltration of adipose tissue by macrophages. The latter, in turn, prevent the transformation of preadipocytes into mature adipocytes, blocking the development of adipose tissue hyperplasia and promoting further hypertrophy of fat cells.

Assuming that chemokines are produced not only in hypertrophied adipocytes but also by macrophages infiltrating adipose tissue, this process acquires the character of a "vicious circle", which is probably maintained and aggravated in the presence of high homocysteine concentrations [17, 19].

IMPAIRED MICROCIRCULATION IN OBESITY AND THE RELATIONSHIP WITH HYPERHOMOCYSTEINAEMIA

In 2004, Trayhurn and Wood were first to propose the idea of obesity-related white adipose tissue hypoxia (WAT) as the cause of adipose tissue dysfunction. Since then, a number of studies have been conducted and there is much debate about the cause of adipose tissue dysfunction associated with hypoxia. These dysfunctions are proposed as a major cause for the development of a pro-inflammatory phenotype of adipose tissue, despite limited data of human studies [20].

Hyperhomocysteinaemia may serve as an additional provocative factor in the development of hypoxia through mechanisms of vascular endothelial dysfunction. Numerous publications

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correlate high plasma homocysteine rates with various pathologies of the vascular tract. Different studies present various mechanisms of homocysteine-induced endothelial dysfunction. Specifically, there is evidence that hyperhomocysteinaemia counteracts the vasodilatory properties of nitric oxide (NO) through the formation of S-nitrosohomocysteine, which contributes to the maintenance and induction of endothelial pathology [21]. Other sources indicate that homocysteine triggers smooth muscle cell proliferation and increases collagen synthesis, which leads to intima thickening and myocyte hypertrophy. Hcy provokes accumulation of reactive oxygen species, as a consequence, endothelial cell damage occurs [22]. Glutathione synthesis is also inhibited in HHcy conditions, resulting in accumulation of extra reactive oxygen species which triggers endothelial damage as well [6, 22].

The combination of the above mentioned processes eventually leads to the development of endothelial dysfunction, impaired microcirculation and hypoxia. Consequently, hypoxia-sensitive genes are expressed, which provokes the attraction of immune cells and the development of aspetic inflammation of adipose tissue [18, 20].

In addition, directly damaging the endothelium, homocysteine promotes the release of cytokines and other inflammatory factors (IL-6, IL-8, TNFα, etc.), which also supports inflammation in adipose tissue [22]. At the same time, the inflammation intensifies the processes of angiogenesis, they become extremely active and subsequently may lead to endothelial dysfunction as well. There is a tendency to form another vicious circle.

RELATIONSHIP BETWEEN HYPERHOMOCYSTEINAEMIA, INSULIN RESISTANCE AND OBESITY

Insulin resistance (IR) positively correlates with hyperhomocysteinaemia in many studies. Generally, this relationship is attributed to impaired liver function in the presence of high blood insulin concentrations (e.g., in non-alcoholic fatty liver disease, which will be discussed later). However, there is a hypothesis that hyperhomocysteinaemia is a factor in the development of IR. This theory is supported by animal studies. To name a few, J. Golbahar et al. conducted a study on two groups of male rats (the test group received Hcy daily with drinking water, the control group did not receive Hcy) in order to confirm the hypothesis that hyperhomocysteinemia may cause hyperinsulinemia leading to insulin resistance in rats. The study evaluated plasma glucose, insulin, total Hcy concentrations, oral glucose tolerance tests in the control and test groups twice (before the study and after 50 days). Based on the results, the mean fasting plasma insulin level was significantly higher in the test group, whereas the mean glucose/insulin rate was significantly lower in the test group than in the control group. In addition, the mean insulin resistance index as assessed by homeostasis was significantly higher in the experimental rats, but the mean plasma glucose levels were not significantly different. Additionally, the results of oral glucose tolerance tests showed the development of insulin resistance in experimental rats after 50-day of homocysteine consumption [23].

Being a strong proinflammatory agent, Hcy provokes the release of a large number of cytokines, including TNFα and IL-6. They can similarly activate the insulin receptor, however, in contrast to a physiological pathway when insulin activates its receptor and phosphorylates tyrosine, cytokines activate serine kinase; accordingly, phosphorylation of another amino acid, serine, is triggered, including the substrate of the insulin receptor (SIR-1). This process inactivates SIR-1 or leads to its destruction by blocking tyrosine phosphorylation in both the insulin receptor and SIR-1, resulting in disruption of the intracellular insulin signaling pathway and insulin's characteristic actions. Thus insulin resistance develops.

However, TNFα stimulates the development of insulin resistance by another mechanism as well. It promotes an increase of free fatty acids in the blood, and this is another pathway for the development of insulin resistance in many tissues [17].

Increasing the concentration of cytokines (IL-1, IL-6, TNFα), homocysteine can probably lead to aggravated expression and secretion of resistin. Resistin is a peptide hormone mainly secreted by adipose tissue. Its effects play a key role in the development of insulin resistance and diabetes associated with obesity [10].

In addition, hyperhomocysteinaemia provokes inflammation in adipose tissue through the secretion of adiponectins and inflammatory mediators (leptin, TNFα, adiponectin, IL-6, IL-8, etc.) which may contribute to the development of IR, as presented above [17, 18].

Therefore, IR leads to a decrease in the synthesis of nitric oxide and prostacyclin and increases the synthesis of vasoconstrictors resulting in the

development of endothelial dysfunction, which was described in the previous section. The formation of another vicious circle is traced [24].

Additionally, there is a theory of primary obesity arising from blood hyperinsulinaemia and insulin resistance of body tissues — the so-called endocrine (carbohydrate-insulin) model of obesity. Deficiency of lipolysis and beta-oxidation in mitochondria against the background of high levels of insulin in the blood underlie the theory. It subsequently leads to energy deficiency, resulting in muscle weakness against the background of increased appetite, and, as a consequence, an increase in body weight [24, 25]. If the theory of hyperhomocysteinemia as a risk factor for the development of insulin resistance is correct, then Hcy may lead to an increase in body mass index through this mechanism. However, there is currently no scientific evidence to support this hypothesis, and further study is required.

HYPERHOMOCYSTEINAEMIA AND NON-ALCOHOLIC FATTY LIVER DISEASE

Recently, there has been increased interest in the positive relationship between homocysteine and the prevalence of nonalcoholic fatty liver disease (NAFLD) [26]. On the one hand, homocysteine is produced and catabolized in the liver. In case of liver damage the levels of Hcy in serum may feasibly increase. One of the possible mechanisms of HHcy is impaired homocysteine trans-sulfation against the background of the negative effect of high insulin concentrations in IR. Deterioration of liver function in obesity due to steatosis leads to a reduced activity of enzymatic systems, which slows down homocysteine metabolism and contributes to hyperhomocysteinaemia [10].

On the other hand, according to foreign studies, there is a suggestion that Hcy may contribute to the progression of liver damage independently. To name a few, in L. Yao et al. (2016) found that hyperhomocysteinaemia could promote liver steatosis in mice through activation of the aryl hydrocarbon receptor pathway. According to several experimental studies, lipid accumulation in the liver was induced in different models of hyperhomocysteinaemia in the Pediatric NAFLD study. In 2014, A. Pastore et al. indicated that Hcy levels strongly correlated with the severity of liver damage. These studies suggest that elevated blood Hcy is associated with the progression of NAFLD [27].

The pathogenesis of NAFLD includes a large number of pathogenetic mechanisms associated with abdominal obesity and IR: oxidative stress, endothelial dysfunction, chronic vascular inflammation, and altered secretion of adipocytokines, especially adiponectin, which increase as pathologic liver changes progress. It should be noted that IR is considered as an independent factor that can determine the development and progression of NAFLD. There are many studies indicating a close relationship between NAFLD and IR of liver, adipose and muscle tissue. Therefore, when metabolically obese but normal weight syndrome (MONW) develops, systemic insulin resistance is indicated in these patients. In light of the well-known association between NAFLD and insulin resistance (IR), NAFLD without obesity can be considered as a "hepatic" phenotype of MONW [28].

As discussed earlier, Hcy probably plays an important role in the development of IR, and it could theoretically participate in the pathogenesis of NAFLD. However, no reliable data supporting this theory have been found by the moment.

CONCLUSION

Thus, there is no doubt that Hcy is involved in many metabolic pathways which lead to the formation/maintenance/progression of hypertention in obesity and related comorbid conditions. However, there is insufficient data to form a unified theory. It is necessary to expand the laboratory practice of Hcy determination in order to collect additional statistical information on the correlation between Hcy, obesity and other conditions.

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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REFERENCES

1. Arkhipova E.V. Metabolicheskiy sindrom: patogenez, kriterii diagnostiki i lecheniye. [Metabolic syndrome: pathogenesis, diagnostic criteria and treatment]. Vestnik BGU. Meditsina i farmatsiya. 2019; 2: 3–9. DOI: 10.18101/2306-1995-2019-2-3-9. (In Russian).
2. Sagitova G.R., Antonova A.A., Davydova O.V. i dr. Morfofunktsional'nyye izme-neniya serdtsa pri ozhirenii. [Morphofunctional changes in the heart in obesity]. Glavvrach Yuga Rossii. 2023; 2(88): 17–8. (In Russian).
3. Mukhamedova N.H., Shukurova U.P., Sobirova M.R. Especially changes gomocysteine in women of childbearing age with metabolic syndrome. European science. 2021; 1(57): 57–60.
4. Arkhipkina T.L., Lyubimova L.P. Gipergomotsisteinemiya, disfunktsiya endoteliya i ikh svyazi s polovymi steroidami pri sindrome polikistoznykh yaichnikov. [Hyperhomocysteinemia, endothelial dysfunction and their relationship with sex steroids in polycystic ovary syndrome]. Zhurnal Akusherstvo, ginekologiya i reproduktsiya. 2016; 3(10): 24–8. DOI: 10.17749/2313-7347.2016.10.2.024-028. (In Russian).
5. Yevdokimova N.V. Risk arterial'noy gipertenzii u detey razlichnogo vozrasta s ozhireniyem. [The risk of arterial hypertension in children of different ages with obesity]. Children's Medicine of the North-West. 2021; 9(4): 55–8. (In Russian).
6. Vasil'yev A.G., Morozova K.V., Brus T.V. i dr. Rol' narusheniy obmena gomotsistei-na v patologicheskikh protsessakh. [The role of homocysteine metabolism disorders in pathological processes]. Rossiyskiye biomeditsinskiye issledovaniya. 2022; 1: 44–59. (In Russian).
7. Firsova L.A., Evdokimova N.V., Novikova V.P. et al. Markers of endothelial dysfunction in children with obesity. University Therapeutic Journal. 2022; 4(S): 135.
8. Ibragimov B.F., Ibragimova N.S. Rol' gomotsisteina v patogeneze sindroma polikistoznykh yaichnikov u zhenshchin. International scientific review. [The role of homocysteine in the pathogenesis of polycystic ovary syndrome in women]. International scientific review. 2020; LXVI: 111–3. (In Russian).
9. Murkamilov I.T., Aytbayev K.A., Fomin V.V. i dr. Gomotsistein i risk nefrotse-rebrovaskulyarnykh zabolevaniy. [Homocysteine and the risk of nephrocerebrovascular diseases]. The Scientific Heritage. 2020; 50: 29–35. (In Russian).
10. Pchelin I.Yu., Marshalko D.V., Shishkin A.N. i dr. Faktory, assotsiirovannyye s gipergomotsisteinemiyey, u patsiyentov s abdominal'nym ozhireniyem. [Factors associated with hyperhomocysteinemia in patients with abdominal obesity]. Kardiologiya v Belarusi. 2019; 11(5): 744–55. (In Russian).
11. Paganelli F., Mottola G., Fromonot J. et al. Hyperhomocysteinemia and Cardiovascular Disease: Is the Adenosinergic System the Missing Link? Int J Mol Sci. 2021; 22(4): 1690. DOI: 10.3390/ijms22041690.
12. Naumov A.V., Danil'chik I.V., Sarana Yu.V. Tri puti remetilirovaniya gomotsi-steina. [Three pathways of homocysteine remethylation]. Zhurnal GrGMU. 2016; 2(54): 27–32. (In Russian).
13. Luksha A.V. Assotsiatsiya polimorfizmov A1298S i S677T gena MTHFR i uroven' gomotsisteina u detey s arterial'noy gipertenziyey. [Association of polymorphisms A1298C and C677T of the MTHFR gene and homocysteine levels in children with arterial hypertension]. Vestnik VGMU. 2023; 22(1): 67–75. DOI: 10.22263/2312-4156.2023.1.67. (In Russian).
14. Sabirova A.V., Volosnikov D.K., Dolinina A.F. i dr. Gomotsisteinemiya — marker mul'tifaktorial'nykh zabolevaniy detskogo vozrasta. [Homocysteinemia is a marker of multifactorial diseases of childhood]. Pediatricheskiy vestnik Yuzhnogo Urala. 2021; 1: 57–67. (In Russian).
15. Dorokhov N.A., Trofimova A.V., Skudarnov Ye.V. i dr. Izmeneniye pokazateley gemo-staza i gomotsisteina na fone displazii soyedinitel'noy tkani u detey. [Changes in hemostasis and homocysteine indices against the background of connective tissue dysplasia in children]. Rossiyskiy vestnik perinatologii i pediatrii. 2021; 66(4): 343. (In Russian).
16. Wang J., You D., Wang H. et al. Association between homocysteine and obesity: A meta-analysis. J Evid Based Med. 2021; 14(3): 208–17. DOI: 10.1111/jebm.12412.
17. Pavlova Z.Sh., Golodnikov I.I. Ozhireniye = vospaleniye. Patogenez. Chem eto grozit muzhchinam? [Obesity = inflammation. Pathogenesis. What does this mean for men?]. Meditsinskiy vestnik Yuga Rossii. 2020; 11(4): 6–23. DOI: 10.21886/2219-8075-2020-11-4-6-23. (In Russian).

18. Simanenkov V.I., Tikhonov S.V., Il'yashevich I.G. i dr. Epidemiologiya, sotsial'nyye aspekty i patogenez ozhireniya. [Epidemiology, social aspects and pathogenesis of obesity]. Vestnik Severo-Zapadnogo gosudarstvennogo meditsinskogo universiteta im. I.I. Mechnikova. 2017; 9(1): 21–7. (In Russian).
19. Wang G., Siow Y.L. Homocysteine induces monocyte chemoattractant protein-1 expression by activating NF-kappaB in THP-1 macrophages. Am. J. Physiol. Heart Circ. Physiol. 2001; 280(6): H2840–7. DOI: 10.1152/ajpheart.2001.280.6.H2840.
20. Hodson L. Adipose tissue oxygenation: Effects on metabolic function. Adipocyte. 2014; 3(1): 75–80. DOI: 10.4161/adip.27114.
21. Kumar A., Palfrey H.A., Pathak R. et al. The metabolism and significance of homocys-teine in nutrition and health. Nutr. Metab. 2017; 14: 78.
22. Stepanova T.V., Ivanov A.N., Popykhova E.B., Lagutina D.D. Molekulyarnyye markery endotelial'noy disfunktsii. [Molecular markers of endothelial dysfunction]. Sovremennyye problemy nauki i obrazovaniya. 2019; 1. Dostupen po: https://s.science-education.ru/pdf/2019/1/28530 (data obrashcheniya 15.06.2023). (In Russian).
23. Golbahar J., Aminzadeh M.A., Kassab S.E., Omrani G.R. Hyperhomocysteinemia induc-es insulin resistance in male Sprague-Dawley rats. Diabetes Res. Clin. Pract. 2007; 76: 1–5. DOI: 10.1186/s12986-017-0233-z.
24. Lavrenova Ye.A., Drapkina O.M. Insulinorezistentnost' pri ozhirenii: prichiny i posledstviya. [Insulin resistance in obesity: causes and consequences]. Ozhireniye i metabolizm. 2020; 17(1): 48–55. DOI: 10.14341/omet9759. (In Russian).
25. Martyushev-Poklad A.V., Yankevich D.S., Petrova M.V., Savitskaya N.G. Dve modeli razvitiya insulinorezistentnosti i strategiya bor'by s vozrastzavisimymi zabo-levaniyami: obzor literatury. [Two models of the development of insulin resistance and a strategy to combat age-related diseases: a review of the literature]. Problemy Endokrinologii. 2022; 68(4): 59–68. DOI: 10.14341/probl13090. (In Russian).
26. Won B.Y., Park K.C., Lee S.H. et al. Sex Difference in the Association between Serum Homocysteine Level and Non-Alcoholic Fatty Liver Disease. Korean J Fam Med. 2016; 37(4): 242–7. DOI: 10.4082/kjfm.2016.37.4.242.
27. Yao L., Wang C., Zhang X. et al. Hyperhomocysteinemia activates the aryl hydrocarbon receptor/CD36 pathway to promote hepatic steatosis in mice. Hepatology. 2016; 64(1): 92–105. DOI: 10.1002/hep.28518.
28. Buyeverov A.O., Bogomolov P.O. Nealkogol'naya zhirovaya bolezn' pecheni bez ozhire-niya: problema, ozhidayushchaya resheniya. [Non-alcoholic fatty liver disease without obesity: a problem awaiting solution]. Terapevticheskiy arkhiv. 2017; 89(12): 226–32. DOI: 10.17116/terarkh20178912226-232. (In Russian).

ЛИТЕРАТУРА

1. Архипова Э.В. Метаболический синдром: патогенез, критерии диагностики и лечение. Вестник БГУ. Медицина и фармация. 2019; 2: 3–9. DOI: 10.18101/2306-1995-2019-2-3-9.
2. Сагитова Г.Р., Антонова А.А., Давыдова О.В. и др. Морфофункциональные изменения сердца при ожирении. Главврач Юга России. 2023; 2(88): 17–8.
3. Mukhamedova N.H., Shukurova U.P., Sobirova M.R. Especially changes gomocysteine in women of childbearing age with metabolic syndrome. European science. 2021; 1(57): 57–60.
4. Архипкина Т.Л., Любимова Л.П. Гипергомоцистеинемия, дисфункция эндотелия и их связи с половыми стероидами при синдроме поликистозных яичников. Журнал Акушерство, гинекология и репродукция. 2016; 3(10): 24–8. DOI: 10.17749/2313-7347.2016.10.2.024-028.
5. Евдокимова Н.В. Риск артериальной гипертензии у детей различного возраста с ожирением. Children's Medicine of the North-West. 2021; 9(4): 55–8.
6. Васильев А.Г., Морозова К.В., Брус Т.В. и др. Роль нарушений обмена гомоцистеина в патологических процессах. Российские биомедицинские исследования. 2022; 1: 44–59.
7. Firsova L.A., Evdokimova N.V., Novikova V.P. et al. Markers of endothelial dysfunction in children with obesity. University Therapeutic Journal. 2022; 4(S): 135.
8. Ибрагимов Б.Ф., Ибрагимова Н.С. Роль гомоцистеина в патогенезе синдрома поликистозных яичников у женщин. International scientific review. 2020; LXVI: 111–3.
9. Муркамилов И.Т., Айтбаев К.А., Фомин В.В. и др. Гомоцистеин и риск нефроцереброваскулярных заболеваний. The Scientific Heritage. 2020; 50: 29–35.
10. Пчелин И.Ю., Маршалко Д.В., Шишкин А.Н. и др. Факторы, ассоциированные с гипергомоцистеинемией, у пациентов с абдоминальным ожирением. Кардиология в Беларуси. 2019; 11(5): 744–55.
11. Paganelli F., Mottola G., Fromonot J. et al. Hyperhomocysteinemia and Cardiovascular Disease: Is the Adenosinergic System the Missing Link?

Int J Mol Sci. 2021; 22(4): 1690. DOI: 10.3390/ijms22041690.
12. Наумов А.В., Данильчик И.В., Сарана Ю.В. Три пути реметилирования гомоцистеина. Журнал ГрГМУ. 2016; 2(54): 27–32.
13. Лукша А.В. Ассоциация полиморфизмов A1298C и C677T гена MTHFR и уровень гомоцистеина у детей с артериальной гипертензией. Вестник ВГМУ. 2023; 22(1): 67–75. DOI: 10.22263/2312-4156.2023.1.67.
14. Сабирова А.В., Волосников Д.К., Долинина А.Ф. и др. Гомоцистеинемия — маркер мультифакториальных заболеваний детского возраста. Педиатрический вестник Южного Урала. 2021; 1: 57–67.
15. Дорохов Н.А., Трофимова А.В., Скударнов Е.В. и др. Изменение показателей гемостаза и гомоцистеина на фоне дисплазии соединительной ткани у детей. Российский вестник перинатологии и педиатрии. 2021; 66(4): 343.
16. Wang J., You D., Wang H. et al. Association between homocysteine and obesity: A meta-analysis. J Evid Based Med. 2021; 14(3): 208–17. DOI: 10.1111/jebm.12412.
17. Павлова З.Ш., Голодников И.И. Ожирение = воспаление. Патогенез. Чем это грозит мужчинам? Медицинский вестник Юга России. 2020; 11(4): 6–23. DOI: 10.21886/2219-8075-2020-11-4-6-23.
18. Симаненков В.И., Тихонов С.В., Ильяшевич И.Г. и др. Эпидемиология, социальные аспекты и патогенез ожирения. Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. 2017; 9(1): 21–7.
19. Wang G., Siow Y.L. Homocysteine induces monocyte chemoattractant protein-1 expression by activating NF-kappaB in THP-1 macrophages. Am. J. Physiol. Heart Circ. Physiol. 2001; 280(6): H2840–7. DOI: 10.1152/ajpheart.2001.280.6.H2840.
20. Hodson L. Adipose tissue oxygenation: Effects on metabolic function. Adipocyte. 2014; 3(1): 75–80. DOI: 10.4161/adip.27114.
21. Kumar A., Palfrey H.A., Pathak R. et al. The metabolism and significance of homocys-teine in nutrition and health. Nutr. Metab. 2017; 14: 78.
22. Степанова Т.В., Иванов А.Н., Попыхова Э.Б., Лагутина Д.Д. Молекулярные маркеры эндотелиальной дисфункции. Современные проблемы науки и образования. 2019; 1. Доступен по: https://s.science-education.ru/pdf/2019/1/28530 (дата обращения 15.06.2023).
23. Golbahar J., Aminzadeh M.A., Kassab S.E., Omrani G.R. Hyperhomocysteinemia induc-es insulin resistance in male Sprague-Dawley rats. Diabetes Res. Clin. Pract. 2007; 76: 1–5. DOI: 10.1186/s12986-017-0233-z.
24. Лавренова Е.А., Драпкина О.М. Инсулинорезистентность при ожирении: причины и последствия. Ожирение и метаболизм. 2020; 17(1): 48–55. DOI: 10.14341/omet9759.
25. Мартюшев-Поклад А.В., Янкевич Д.С., Петрова М.В., Савицкая Н.Г. Две модели развития инсулинорезистентности и стратегия борьбы с возрастзависимыми заболеваниями: обзор литературы. Проблемы эндокринологии. 2022; 68(4): 59–68. DOI: 10.14341/probl13090.
26. Won B.Y., Park K.C., Lee S.H. et al. Sex Difference in the Association between Serum Homocysteine Level and Non-Alcoholic Fatty Liver Disease. Korean J Fam Med. 2016; 37(4): 242–7. DOI: 10.4082/kjfm.2016.37.4.242.
27. Yao L., Wang C., Zhang X. et al. Hyperhomocysteinemia activates the aryl hydrocarbon receptor/CD36 pathway to promote hepatic steatosis in mice. Hepatology. 2016; 64(1): 92–105. DOI: 10.1002/hep.28518.
28. Буеверов А.О., Богомолов П.О. Неалкогольная жировая болезнь печени без ожирения: проблема, ожидающая решения. Терапевтический архив. 2017; 89(12): 226–32. DOI: 10.17116/terarkh20178912226-232.

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LUNGS AS A TARGET FOR VITAMIN D AND PHOSPHATONINES

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Abstract. Vitamin D axis — fibroblast growth factor 23 (FGF23) — the klotho protein plays an important role in ontogenesis and functioning of the respiratory system. There is evidence of the connection of vitamin D with phosphatonines — a complex of phosphatic substances that stimulates the withdrawal of phosphates through the kidneys. Vitamin D receptor (NDR) is found in animal models in virtually all lung cell types. In cells of the airway epithelium, there is not only HDR, but also enzymes that activate and degrade its metabolites. The involvement of vitamin D and the main components of the phosphatonin complex in inflammatory diseases of the respiratory system has been proven. Studying the actions of the $1,25(OH)_2$ — FGF23 — protein klotho system and the control capabilities of this system is key to the development of new therapeutic interventions in pulmonology.

Key words: *vitamin D; respiratory system; fibroblast growth factor — FGF; klotho protein; phosphatonins.*

ЛЕГКИЕ КАК МИШЕНЬ ДЛЯ ВИТАМИНА D И ФОСФАТОНИНОВ

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Резюме. Ось «витамин D — фактор роста фибробластов 23 (fibroblast growth factor, FGF23) — белок klotho» играет важную роль в онтогенезе и функционировании дыхательной системы. Приведены доказательства связи витамина D с фосфатонинами — комплексом фосфатурических субстанций, стимулирующим вывод фосфатов через почки. Рецептор витамина D (ВДР) на моделях животных обнаружен практически во всех типах клеток легкого. В клетках эпителия дыхательных путей существует не только ВДР, но и ферменты, осуществляющие активацию и деградацию его метаболитов. Доказано участие витамина D и основных компонентов комплекса фосфатонинов в воспалительных заболеваниях дыхательной системы. Изучение действий системы «$1,25(OH)_2$ — FGF23 — белок klotho» и возможностей управления этой системой является ключом к разработке новых терапевтических вмешательств в пульмонологии.

Ключевые слова: *витамин D; дыхательная система; фактор роста фибробластов — FGF; белок klotho; фосфатонины.*

Vitamin D is mainly involved in maintaining phosphorus and calcium homeostasis. However, modern research has revealed it also effects on a number of cellular processes including cell proliferation, differentiation, wound healing, repair and regulatory systems, immunity and inflammation. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2$), is known to promote mucosal barrier integrity, destroy pathogens (via induction of antimicrobial peptides), and modulate inflammation and immune responses.

INTRODUCTION

The vitamin D — fibroblast growth factor 23 (FGF23) — klotho protein axis is well known for its role in maintaining phosphorus and calcium homeostasis [1]. The airway mucosa is an important site of local synthesis, degradation and signaling of $1,25(OH)_2$. The expression of vitamin D receptor by different cell types in the lung and the fact that these cells respond to vitamin D or can locally produce vitamin D, proves that the lungs represent a target for vitamin D action [2]. Vitamin D deficiency is associated with various diseases, including chronic inflammatory lung diseases, namely asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) [3–5]. Animal model studies have shown that maternal vitamin D deficiency can impair lung development, structure, and function in offspring; it is hypothesized that maternal serum 25(OH)D levels are important for healthy fetal lung development. It may be relevant because associations have been found between the reduced pulmonary function in children and the development of COPD later in life [6]. In addition, 25(OH)D circulating in the mother's body influences the gut microbiota and therefore may indirectly modulate immune responses in the lung via the gut-lung axis [7]. These observations suggest an important role for vitamin D during fetal and postnatal lung maturation and dempnstrate that adequate levels of 25(OH)D may contribute to protection against childhood asthma and, possibly, COPD in older age.

In 1994, the existence of a complex of phosphaturic factors (phosphatonins) was described. They cause phosphate loss by the kidneys. The currently known phosphatonins include fibroblast growth factor (FGF23), matrix extracellular phosphoglycoprotein (MEPE), secreted frizzled related protein 4 (sFRP4), and fibroblast growth factor 7 (FGF7) [8]. The close relationship and mutual influence of phosphatonins and vitamin D have been proven. The role of these metabolites in the pathogenesis of a number of diseases, primarily renal, cardiovascular, and pulmonary diseases, is being intensively studied.

A complex of phosphaturic proteins, the *phosphatonins*, downregulate phosphate balance through direct inhibition of its reabsorption in the proximal tubule and indirectly through suppression of $1,25(OH)_2$ production in the kidney. There are four components included in the phosphatonin group, FGF23 is the best studied.

FGF23 is predominantly expressed in bone (osteocytes and osteoblasts). FGF23 production is stimulated by multiple factors, including high dietary or serum phosphate levels, parathyroid hormone (PTH), $1,25(OH)_2$, calcium, iron deficiency, erythropoietin, metabolic acidosis, and inflammatory cytokines. In order to effect phosphorus balance FGF23 requires the co-receptor α-klotho, which is mainly produced in the kidney and the parathyroid gland. As for the kidney, klotho is expressed in distal tubules and less abundantly in proximal tubules. α-klotho is a transmembrane protein that exists both in a membrane-bound form acting as a co-receptor for FGF23 and in a secreted soluble form found in the blood, exerting endocrine and paracrine actions in distant organs [9]. Excessive FGF23 causes hypophosphataemia by decreasing NaPi transport activity and suppressing $1,25(OH)_2$ production, whereas FGF23 deficiency causes hyperphosphataemia and elevates $1,25(OH)_2$ levels. α-klotho functions as a co-receptor for FGF23; its production is increased in response to elevated $1,25(OH)_2$ levels. This protein causes phosphaturia by inhibiting the renal NaPi-IIa transporter [10]. The function of fibroblast growth factor FGF23 is far beyond its canonical function as a regulator of mineral metabolism. FGF23 is implicated in the pathogenesis of several diseases, including chronic complications associated with kidney disease, cardiovascular disease, and obesity-related disorders [11]. The presence of four FGF receptor isoforms in the lung and the ability of FGF23 to stimulate lung cells support the concept that the lung is a target for FGF23, whereas the contribution of klotho remains to be clarified [12].

Matrix extracellular phosphoglycoprotein MEPE administered intraperitoneally causes hyperphosphaturia and hypophosphataemia in mice. MEPE inhibits phosphate uptake by human proximal tubule epithelial cells *in vitro*. In addition, MEPE in-

hibits bone mineralization in vitro. Mice with zero MEPE show increased bone mineralization [13].

In experiments on opossums, *secreted Frizzled related protein 4 (sFRP4)*, has been shown to inhibit sodium-dependent phosphate transport by reducing NaPi-2a content in the brush border membrane of proximal tubules and on the surface of renal epithelial cells. Generally, although sFRP4 dramatically alters phosphate transport in the kidney and possibly the physiology of $1,25(OH)_2$, most data indicate that it plays a minor role in the regulation of phosphate homeostasis [14].

Fibroblast growth factor 7 (FGF7) reduces sodium-dependent phosphate transport in opossum kidney epithelial cells and enhances phosphaturia in rats. A recent study showed that low serum FGF7 levels were observed in children with hypophosphatasia and hyperphosphatemia [15].

VITAMIN D AND PHOSPHATONINS IN RESPIRATORY SYSTEM CELLS

The presence of vitamin D receptor (VDR) in animal models can be detected in the last stages of pregnancy and after birth in practically all types of lung cells — on airway epithelial and smooth muscle cells, on type 2 alveolar cells, on alveolar macrophages, on fibroblasts, as well as on blood cells, including neutrophils, monocytes, NK cells, eosinophils, T- and B-lymphocytes, and mast cells [16]. Recently, it was shown that VDRs are localized in apical bronchial epithelial cells and are completely absent in basal epithelial cells and in vascular endothelial cells [17]. Studies have established the influence of genetic polymorphisms of VDR (BsmI, FokI, TaqI, ApaI) which amplify the risk of development of chronic allergic lung diseases and COPD. At the same time, the study of phenotypic influence of FokI polymorphism of VDR gene on the course of chronic nonspecific lung diseases (CNLD) in children showed no statistically significant association [18].

Due to the presence of the CYP27B1 enzyme, the active form of vitamin D ($1,25(OH)_2$) is synthesized in airway epithelial cells, in stimulated macrophages, and in B-lymphocytes. Restriction of endogenous formation of $1,25(OH)_2$ is apparently accomplished by the presence of the enzyme CYP24A2 in some cells, which converts the active form of vitamin D to the inactive form. CYP24A2 is found in type 2 alveolar cells, in airway epithelial cells; its inactive form has been detected in alveolar macrophages [12].

FGF23 is expressed in adult mouse and human lung tissue [19, 20], although the cell types that produce FGF23 have not yet been identified. There is no consensus on the presence of α-klotho in lung tissue. In humans, this protein is distributed along the airway epithelium [21]. A recent study using specific antibodies showed that the lungs do not endogenously express native α-klotho protein, but rather obtain it from the bloodstream [22].

The currently available information on the nature of the effect of vitamin D, FGF23 and α-klotho on various processes in the lung is presented in Table 1.

Table 1. Overview of the Actions of Vitamin D, FGF23, and α-klotho in the Lung (adopted from [16])

Таблица 1. Роль витамина D, FGF23 и α-klotho в различных процессах, связанных с легкими (адаптировано из [16])

Process	Vitamin D	FGF23	α-klotho
Fetal development	Lung maturation	Structural integrity	Structural integrity "Anti-senescence"
Innate/adaptive immunity	Positive modulation	Not known	Not known
Infection	Modulation phagocytosis Antibacterial Antiviral Antimicrobial	Not known	Not known
Inflammation	Anti-inflammatory	Pro-inflammatory	Anti-inflammatory
Oxidative stress	Antioxidant	No action	Antioxidant
Remodeling/damage	Antifibrotic Antiproliferative Antiprotease	Antifibrotic	Antifibrotic
Epithelial barrier	Maintenance integrity	Not known	Not known

ROLE OF VITAMIN D AND PHOSPHATONINS IN THE DEVELOPMENT OF LUNG IN ONTOGENESIS

The fetus does not produce 25(OH). 25(OH) passes through the placenta. The placenta absorbs 25(OH) by endocytosis. An important component of calcium homeostasis during pregnancy is calcitonin. It promotes transcription of the CYP27B1 gene and may therefore be a key determinant of placental vitamin D metabolism. 25(OH) is transformed into both inactive 24,25-dihydroxyvitamin D_3 and active 1,25-dihydroxyvitamin D ($1,25(OH)_2$) in the placenta, consequently, these metabolites release into both maternal and fetal circulation [23]. Vitamin D supply to the fetus does not solely depend on maternal vitamin D status but on placental functioning as well.

Transfer of 25(OH) through the placenta mainly occurs during the last trimester, meaning that preterm newborns are particularly at risk of vitamin D deficiency.

The effect of low maternal vitamin D levels during pregnancy and its role in fetal lung development and maturation, as well as susceptibility to lung disease in the postnatal period, is currently being investigated. This issue is very relevant as hypovitaminosis D is common in pregnant women and newborns.

The presence of VDR in fetal lungs during the last quarter of pregnancy and the activation of vitamin D regulatory enzymes just before birth confirm the potential role of vitamin D in the late stage of normal fetal lung development [24]. The appearance of VDR during gestation coincides with the time of the onset of type 2 pneumocyte differentiation and the beginning of surfactant secretion, typical signs of lung maturation. In vitro studies on fetal rat lung cultures and freshly isolated cells have shown that exogenous $1,25(OH)_2$ accelerates functional maturation of type 2 pneumocytes by decreasing their glycogen content and increasing surfactant synthesis and secretion. Type 2 alveolar cells were actually identified as specific targets for $1,25(OH)_2$ during fetal lung maturation, as these cells responded to exogenous $1,25(OH)_2$ by increasing VDR expression. Fetal lung fibroblasts do not express VDR, but they are able to convert $25(OH)D_3$ to $1,25(OH)_2$, unlike type 2 alveolar cells [12].

Several studies have shown that maternal vitamin D deficiency during pregnancy is associated with postnatal lung function impairment after birth [25], in particular with an increased risk of asthma. Moreover, low levels of 25-hydroxyvitamin D in cord blood of preterm newborns have been associated with an increased incidence of respiratory infections in infancy [26]. However, these data require verification. The association between vitamin D administration during pregnancy and the risk of bronchial asthma in born children was not confirmed at 6-year follow-up [27]. In a study to determine the association of vitamin D levels with endogenous microbial peptides (cathelicidin LL-37 and HBD-2) in congenital pneumonia in preterm newborns, it was shown that low vitamin D concentration may be associated with congenital pneumonia. Vitamin D levels may also predict the need for artificial ventilation and the duration of hospitalization for congenital pneumonia in preterm newborns [28].

It is not known whether fetal lungs can be a target for FGF23. However, experimental data do not allow us to deny the role of FGF23 and klotho in lung development. Indeed, mice lacking FGF23 develop emphysema that appears as early as 3 weeks of age and resembles emphysema found in an aged population, consistent with the premature aging phenotypes in these mice. Vitamin D has been shown to partially mediate this process. The first signs of emphysematous in homozygous mutant klotho (KL-/-) mice began to appear at 4 weeks of age and progressed with age until premature death at 8 to 10 weeks of age. Taken together, these data indicate that FGF23 plays an important role in premature lung aging and that klotho gene expression is important for maintaining lung integrity in the postnatal period [12].

ROLE OF VITAMIN D AND PHOSPHATONINS IN RESPIRATORY SYSTEM PATHOLOGY

The production of biologically active $1,25(OH)_2$ is tightly regulated to maintain optimal levels of calcium (Ca^{2+}) and phosphate (PO_4^2 — PO_4^2) for bone mineralization, whereas locally produced (autocrine) $1,25(OH)_2$ in mucosal tissues, and signal transduction may be increased or decreased under the influence of inflammatory mediators, pathogens or inhaled toxins [29]. It may be important since the airway mucosa of patients suffering from chronic inflammatory lung disease is constantly exposed to these factors [30].

The anti-inflammatory effects of vitamin D in the lungs have been proven by studies on cells derived from animals and from human lavage fluid *in vitro*. After dendritic cells, alveolar macrophages, epithelial and smooth muscle cells of

the airways were affected by various stimuli, they reduced the production of proinflammatory cytokines and chemokines under the influence of vitamin D. Anti-inflammatory contribution of vitamin D *in vivo* have been proven in animal models. Vitamin D deficiency aggravates and prolongs lung inflammation, increases amounts of neutrophils in bronchoalveolar lavage after inoculation with *Aspergillus fumigates* [31], as well as with exposure to cigarette smoke [32]. The fact that intratracheal administration of vitamin D in mice had a more pronounced anti-inflammatory effect than oral administration seems to be practically important [16].

The role of FGF23 in the development of lung inflammation and the anti-inflammatory properties of α-klotho are reflected in few studies. Plasma FGF23 levels are elevated in lung diseases characterized by chronic inflammation, such as cystic fibrosis [33] and COPD [34].

Patients with COPD had elevated plasma FGF23 levels which coincided with high levels of inflammatory cytokines in lung and plasma and positively correlated with serum IL-6 levels. However, FGF23 levels were not correlated with disease severity. The authors attribute it to a "burnout" when the residual mass of viable pulmonary epithelium, which serves as a target for FGF23/klotho action, decreases. Thus, changes in the FGF23/klotho correspondance may serve as a marker of the disease, but to a less extent as a marker of its severity [35].

In patients with cystic fibrosis, elevated plasma FGF23 levels were combined with TGF-β-mediated airway inflammation. The proinflammatory role of FGF23 in lung disease can be considered proven; meanwhile there is evidence that klotho has anti-inflammatory activity. Overexpression or supplementation of klotho was able to reduce IL-8 secretion induced by TGF-β and FGF23 in bronchial epithelial cells of cystic fibrosis patients. Blocking klotho in bronchial epithelial cells resulted in increased formation of inflammatory cytokines such as IL-6, IL-8 and MCP-, which points to a role of endogenous klotho in human bronchial inflammation [33].

The klotho protein provides a protective effect against chronic inflammation and therefore may slow the progression of lung diseases characterized by chronic inflammation. This is proved by the following facts. Patients with idiopathic pulmonary fibrosis or COPD have low plasma levels of soluble klotho and high levels of FGF23[34]. α-klotho secretion is decreased after exposure to cigarette smoke on bronchial epithelial cells derived from COPD patients [21, 35]. The expression of α-klotho is reduced in the lungs of healthy smokers compared to nonsmokers [21], as well as in primary interstitial lung fibroblasts from patients with idiopathic pulmonary fibrosis [34]. A significant association between serum klotho level (s-klotho) and well-known biomarkers of inflammation — uric acid, C-reactive protein, leukocyte number and average platelet volume have been found. The correlation between uric acid and s-klotho was the strongest among four markers. The level of s-klotho implies a general inflammatory status; therefore, s-klotho serves as a potential biomarker that inversely correlates with inflammatory conditions [36].

The antibacterial properties of vitamin D have been demonstrated in several studies showing its ability to participate in the destruction of Gram-negative bacteria (untyped *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Bordetella bronchiseptica*) in respiratory epithelial cells [37].

Vitamin D can enhance antimicrobial defense by stimulating the production of antimicrobial peptides such as cathelicidin (LL-37). These antimicrobial peptides contain a vitamin D-sensitive element in the promoter region of their genes and are activated upon vitamin D stimulation. Several *in vitro* studies have confirmed that vitamin D enhances cathelicidin expression in human bronchial epithelial cells (NHBE, 16HBE) derived from donors and COPD patients [38], as well as in alveolar macrophages from smokers and nonsmokers [39]. These data indicate that bacterial or viral infection in lung tissue is probably a potential target for vitamin D, which may contribute to pathogen elimination and reduction of an inflammatory response. No studies could be found to answer the question whether infection in the respiratory system could be a target for FGF23 or klotho.

Some *in vitro* and *in vivo* studies have shown that vitamin D can influence oxidative stress in the lungs. A mouse model of asthma demonstrated that vitamin D normalizes elevated levels of malonic dialdehyde and reduces superoxide dismutase and glutathione activities to control levels. It also increases levels of NF-E2-related factor 2 (Nrf2), a cellular sensor of oxidative stress associated with transcriptional activation of antioxidant response element genes. Moreover, Vitamin D reduces oxidative DNA damage and regulates cellular apoptosis [40]. FGF23 itself is not

involved in protection against oxidative stress, unlike α-klotho, which can directly protect human lung epithelial cells (A459 and primary alveolar type I cells) from oxidative damage and apoptosis induced by hyperoxia and phosphotoxicity by reducing lipid and protein content [41].

Vitamin D probably plays an important role in maintaining the epithelial barrier integrity in the lung. Studies on the bronchial epithelial cell line 16HBE showed that vitamin D is able to counteract cigarette smoke-induced epithelial barrier breakdown by preventing a decrease in transepithelial electrical resistance, increased permeability, and degradation of E-cadherin and β-catenin [42]. It is indicative that vitamin D also increases the expression of transmembrane conductance regulator in human bronchial epithelial cells in cystic fibrosis. This effect was also observed after local administration of vitamin D in vivo by intranasal administration to mice [43]. Whether FGF23/klotho can affect the integrity of the lung epithelial barrier remains to be elucidated.

CONCLUSIONS

Vitamin D is essential for the development of the respiratory system during gestation. Vitamin D has mainly beneficial effects on the lung in the postnatal period, they include immunomodulatory, anti-inflammatory, anti-infectious and antioxidant effects, as well as maintenance of airway structure and epithelial barrier integrity. One of the aspects that is still poorly understood is the ability of some lung cells to respond to exogenous vitamin D and/or to produce active vitamin D. More research is needed, since local direct administration of active vitamin D could enhance the beneficial effects in the respiratory pathology.

In vitro and animal studies show that FGF23 acts as a deleterious agent, increasing inflammation in a variety of chronic lung diseases. Many of these effects are counterbalanced by klotho, which clearly protects the lung from inflammation, oxidative stress, and apoptosis. Studying the "$1,25(OH)_2$ — FGF23 — klotho" system and its possibilities to control this system may be a key to the development of new therapeutic interventions in pulmonology.

ADDITIONAL INFORMATION

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

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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REFERENCES

1. Portales-Castillo I., Simic P. PTH, FGF-23, Klotho and Vitamin D as regulators of calcium and phosphorus: Genetics, epigenetics and beyond. Front Endocrinol (Lausanne). 2022; 13: 992666. DOI: 10.3389/fendo.2022.992666.
2. Gayan-Ramirez G. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho JBMR Plus. 2021; 512: e10569. DOI: 10.1002/jbm4.10569.
3. Belykh N.A., Piznyur I.V. Sovremennyye predstavleniya o roli vitamina D v patogeneze bronkhial'noy astmy u detey. [Modern ideas about the role of vitamin D in the pathogenesis of bronchial asthma in children]. Nauka molodykh (Eruditio Juvenium). 2020; 8(4): 617–28. DOI: 10.23888/HMJ202084617-628. (In Russian).
4. Averina I.A., Sergiyenko D.F. Vliyaniye vitamina D na techeniye khronicheskikh zabolevaniy legkikh u detey. [The effect of vitamin D on the course of chronic lung diseases in children]. Farmateka. 2020; 27(14): 81–6. DOI 10.18565/pharmateca.2020.14.81-86. EDN LISQVX. (In Russian).
5. Averina I.A., Sergiyenko D.F. Izmeneniya pokazateley syvorotochnogo 25 (ON) D u detey s mukovistsidozom. [Changes in serum 25(OH)D levels in children with cystic fibrosis]. Aktual'nyye voprosy sovremennoy meditsiny: materialy III Mezhdunarodnoy konferentsii Prikaspiyskikh

gosudarstv, Astrakhan', 4–5 oktyabrya 2018 goda. Astrakhan': Astrakhanskiy gosudarstvennyy meditsinskiy universitet. 2018: 12–3. EDN YYLNJJ. (In Russian).
6. Bui D.S., Burgess J.A., Lowe A.J. et al. Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap syndrome. Am J Respir Crit Care Med. 2017; 196: 39–46. DOI: 10.1164/rccm.201606-1272OC.
7. Limketkai B.N., Mullin G.E., Limsui D., Parian A.M. Role of Vitamin D in inflammatory bowel disease. Nutr Clin Pract. 2017; 32: 337–45. DOI: 10.1177/0884533616674492.
8. Kritmetapak K., Kumar R. Phosphatonins: From Discovery to Therapeutics. Endocr Pract. 2023; 29(1): 69–79. DOI: 10.1016/j.eprac.2022.09.007.
9. Olauson H., Mencke R., Hillebrands J.L., Larsson T.E. Tissue expression and source of circulating αKlotho. Bone. 2017; 100: 19–35. DOI: 10.1016/j.bone.2017.03.043.
10. Ho B.B., Bergwitz C. FGF23 signaling and physiology. J Mol Endocrinol. 2021; 66: R23eR32.
11. Masanobu Kawai. The FGF23/Klotho axis in the regulation of mineral and metabolic homeostasis. Horm Mol Biol Clin Investig. 2016; 28(1): 55–67. DOI: 10.1515/hmbci-2015-006.
12. Gayan-Ramirez G. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho JBMR Plus. 2021; 5(12): e10569. DOI: 10.1002/jbm4.10569.
13. Bresler D., Bruder J., Mohnike K. et al. Serum MEPE-ASARM-peptides are elevated in X-linked rickets (HYP): implications for phosphaturia and rickets. J Endocrinol. 2004; 183: R1eR9.
14. Kittrawee Kritmetapak, Rajiv Kumar Phosphatonins: From Discovery to Therapeutics. Endocrine Practice journal homepage: www.endocrinepractice.org, https://doi.org/10.1016/j.eprac.2022.09.007.
15. Whyte M.P., Zhang F., Wenkert D. et al. Hyperphosphatemia with low FGF7 and normal FGF23 and sFRP4 levels in the circulation characterizes pediatric hypophosphatasia. Bone. 2020; 134: 115300.
16. Gayan-Ramirez G., Janssens W. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho. JBMR Plus. 2021; 5(12): e10569. DOI: 10.1002/jbm4.10569.
17. Mathyssen C., Aelbrecht C., Serré J. et al. Local expression profiles of vitamin D-related genes in airways of COPD patients. Respir Res. 2020; 21(1): 137. DOI: 10.1186/s12931-020-01405-0.
18. Averina I.A., Sergiyenko D.F. Techeniye khronicheskikh zabolevaniy legkikh u detey v prizme polimorfizma FokI gena VDR. [The course of chronic lung diseases in children in the prism of the FokI polymorphism of the VDR gene]. Farmateka. 2020; 27(9): 81–5. DOI: 10.18565/pharmateca.2020.9.81-85. EDN VESEEH. (In Russian).
19. Krick S., Grabner A., Baumlin N. et al. Fibroblast growth factor 23 and Klotho contribute to airway inflammation. Eur Respir J. 2018; 52: 1800236. DOI: 10.1183/13993003.00236-2018.
20. Barnes J.W., Duncan D., Helton S. et al. Role of fibroblast growth factor 23 and klotho cross talk in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2019; 317: L141–54. DOI: 10.1152/ajplung.00246.2018.
21. Gao W., Yuan C., Zhang J. et al. Klotho expression is reduced in COPD airway epithelial cells: effects on inflammation and oxidant injury. Clin Sci (Lond). 2015; 129: 1011–23.
22. Zhang J., Cao K., Pastor J.V. et al. Alpha-Klotho, a critical protein for lung health, is not expressed in normal lung. FASEB Bio Advances. 2019; 1: 675–87. DOI: 10.1096/fba.2019-00016.
23. Ashley B. et al. Placental uptake and metabolism of 25(OH) vitamin D determine its activity within the fetoplacental unit. eLife. 2022. DOI: 10.7554/eLife.71094.
24. Mandell E., Seedorf G.J., Ryan S. et al. Antenatal endotoxin disrupts lung vitamin D receptor and 25-hydroxyvitamin D 1α-hydroxylase expression in the developing rat. Am J Physiol Lung Cell Mol Physiol. 2015; 309: L1018–26.
25. Hart P.H., Lucas R.M., Walsh J.P. et al. Vitamin D in fetal development: findings from a birth cohort study. Pediatrics. 2015; 135: e167–73.
26. Feng H., Xun P., Pike K. et al. In utero exposure to 25 hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: a meta-analysis of birth cohort studies. J Allergy Clin Immunol. 2017; 139: 1508–17.
27. Augusto A Litonjua, Vincent J Carey, Nancy Laranjo et al. Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction. N Engl J Med. 2020; 382(6): 525–33 DOI: 10.1056/NEJMoa1906137.
28. Zhuravleva L.N., Novikova V.I. Vitamin D i antimikrobnyye peptidy pri vrozhdennoy pnevmonii u nedonoshennykh novorozhdennykh. [Vitamin D and antimicrobial peptides for congenital pneumonia in premature newborns]. Immunopatologiya, allergologiya, infektologiya. 2021; 1: 13–9. DOI: 10.14427/jipai.2021.1.13. EDN ASHJTU. (In Russian).

29. Britt RDJ., Faksh A., Vogel E.R. et al. Vitamin D attenuates cytokine-induced remodeling in human fetal airway smooth muscle cells. J Cell Physiol. 2015; 230: 1189–98. DOI: 10.1002/jcp.24953.
30. Zhang J., Cao K., Pastor J.V. et al. Alpha-Klotho, a critical protein for lung health, is not expressed in normal lung. FASEB BioAdvances. 2019; 1: 675–87. DOI: 10.1096/fba.2019-00016.
31. Li P., Xu X., Cao E. et al. Vitamin D deficiency causes defective resistance to Aspergillus fumigates in mice via aggravated and sustained inflammation. PLoS One. 2014; 9: e99805. DOI: 10.1371/journal.pone.0099805.
32. Heulens N., Korf H., Cielen N. et al. Vitamin D deficiency exacerbates COPD-like characteristics in the lungs of cigarette smoke-exposed mice. Respir Res. 2015; 16: 110. DOI: 10.1186/s12931-015.
33. Krick S., Baumlin N., Aller S.P. et al. Klotho inhibits interleukin-8 secretion from cystic fibrosis airway epithelia. Sci Rep. 2017; 7: 14388. DOI: 10.1038/s41598-017-14811.
34. Barnes J.W., Duncan D., Helton S. et al. Role of fibroblast growth factor 23 and klotho cross talk in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2019; 317: L141–54. DOI: 10.1152/ajplung.00246.2018.
35. Krick S., Grabner A., Baumlin N. et al. Fibroblast growth factor 23 and Klotho contribute to airway inflammation. Eur Respir J. 2018; 52: 1800236. DOI: 10.1183/13993003.00236-2018.
36. Shou-En Wu., Wei-Liang Chen Soluble klotho as an effective biomarker to characterize inflammatory states Ann Med. 2022; 54(1): 1520–9. DOI: 10.1080/07853890.2022.2077428.
37. Chaeuk Chung, Prashanta Silwal, Insop Kim et al. Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. Immune Netw. 2020; 20(2): e12. English. Published online Feb 11, 2020. https://doi.org/10.4110/in.2020.20.e12.
38. Schrumpf J.A., Amatngalim G.D., Veldkamp J.B. et al. Proinflammatory cytokines impair vitamin D-induced host defense in cultured airway epithelial cells. Am J Respir Cell Mol Biol. 2017; 56: 749–76. DOI: 10.1183/13993003.01009-2017.
39. Heulens N., Korf H., Mathyssen C. et al. 1,25 Dihydroxyvitamin D modulates antibacterial and inflammatory response in human cigarette smoke exposed macrophages. PLoS One. 2016; 11: e0160482. DOI: 10.1371/journal.pone.0160482.
40. Wang Z., Zhang H., Sun X., Ren L. The protective role of vitamin D_3 in a murine model of asthma via the suppression of TGF-β/Smad signaling and activation of the Nrf2/HO-1 pathway. Mol Med Rep. 2016; 14: 2389–96.
41. Ravikumar P., Ye J., Zhang J. et al. Klotho protects against oxidative damage in pulmonary epithelia. Am J Physiol Lung Cell Mol Physiol. 2014; 307: L566–75.
42. Zhang R., Zhao H., Dong H. et al. 1α,25-Dihydroxyvitamin D_3 counteracts the effects of cigarette smoke in airway epithelial cells. Cell Immunol. 2015; 295: 137–14.
43. DiFranco K.M., Mulligan J.K., Sumal A.S., Diamond G. Induction of CFTR gene expression by $1,25(OH)_2$ vitamin D_3, 25OH vitamin D_3, and vitamin D_3 in cultured human airway epithelial cells and in mouse airways. J Steroid Biochem Mol Biol. 2017; 173: 323–32.

ЛИТЕРАТУРА

1. Portales-Castillo I., Simic P. PTH, FGF-23, Klotho and Vitamin D as regulators of calcium and phosphorus: Genetics, epigenetics and beyond. Front Endocrinol (Lausanne). 2022; 13: 992666. DOI: 10.3389/fendo.2022.992666.
2. Gayan-Ramirez G. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho JBMR Plus. 2021; 512: e10569. DOI: 10.1002/jbm4.10569.
3. Белых Н.А., Пизнюр И.В. Современные представления о роли витамина D в патогенезе бронхиальной астмы у детей. Наука молодых (Eruditio Juvenium). 2020; 8(4): 617–28. DOI: 10.23888/HMJ202084617-628.
4. Аверина И.А., Сергиенко Д.Ф. Влияние витамина D на течение хронических заболеваний легких у детей. Фарматека. 2020; 27(14): 81–6. DOI: 10.18565/pharmateca.2020.14.81-86. EDN LISQVX.
5. Аверина И.А., Сергиенко Д.Ф. Изменения показателей сывороточного 25(OH)D у детей с муковисцидозом. Актуальные вопросы современной медицины: материалы III Международной конференции Прикаспийских государств, Астрахань, 4–5 октября 2018 года. Астрахань: Астраханский государственный медицинский университет. 2018: 12–3. EDN YYLNJJ.
6. Bui D.S., Burgess J.A., Lowe A.J. et al. Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap syndrome. Am J Respir Crit Care Med. 2017; 196: 39–46. DOI: 10.1164/rccm.201606-1272OC.
7. Limketkai B.N., Mullin G.E., Limsui D., Parian A.M. Role of Vitamin D in inflammatory bowel disease. Nutr Clin Pract. 2017; 32: 337–45. DOI: 10.1177/0884533616674492.

8. Kritmetapak K., Kumar R. Phosphatonins: From Discovery to Therapeutics. Endocr Pract. 2023; 29(1): 69–79. DOI: 10.1016/j.eprac.2022.09.007.
9. Olauson H., Mencke R., Hillebrands J.L., Larsson T.E. Tissue expression and source of circulating αKlotho. Bone. 2017; 100: 19–35. DOI: 10.1016/j.bone.2017.03.043.
10. Ho B.B., Bergwitz C. FGF23 signaling and physiology. J Mol Endocrinol. 2021; 66: R23eR32.
11. Masanobu Kawai. The FGF23/Klotho axis in the regulation of mineral and metabolic homeostasis. Horm Mol Biol Clin Investig. 2016; 28(1): 55–67. DOI: 10.1515/hmbci-2015-006.
12. Gayan-Ramirez G. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho JBMR Plus. 2021; 5(12): e10569. DOI: 10.1002/jbm4.10569.
13. Bresler D., Bruder J., Mohnike K. et al. Serum MEPE-ASARM-peptides are elevated in X-linked rickets (HYP): implications for phosphaturia and rickets. J Endocrinol. 2004; 183: R1eR9.
14. Kittrawee Kritmetapak, Rajiv Kumar Phosphatonins: From Discovery to Therapeutics. Endocrine Practice journal homepage: www.endocrinepractice.org, https://doi.org/10.1016/j.eprac.2022.09.007.
15. Whyte M.P., Zhang F., Wenkert D. et al. Hyperphosphatemia with low FGF7 and normal FGF23 and sFRP4 levels in the circulation characterizes pediatric hypophosphatasia. Bone. 2020; 134: 115300.
16. Gayan-Ramirez G., Janssens W. Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho. JBMR Plus. 2021; 5(12): e10569. DOI: 10.1002/jbm4.10569.
17. Mathyssen C., Aelbrecht C., Serré J. et al. Local expression profiles of vitamin D-related genes in airways of COPD patients. Respir Res. 2020; 21(1): 137. DOI: 10.1186/s12931-020-01405-0.
18. Аверина И.А., Сергиенко Д.Ф. Течение хронических заболеваний легких у детей в призме полиморфизма FokI гена VDR. Фарматека. 2020; 27(9): 81–5. DOI 10.18565/pharmateca.2020.9.81-85. EDN VESEEH.
19. Krick S., Grabner A., Baumlin N. et al. Fibroblast growth factor 23 and Klotho contribute to airway inflammation. Eur Respir J. 2018; 52: 1800236. DOI: 10.1183/13993003.00236-2018.
20. Barnes J.W., Duncan D., Helton S. et al. Role of fibroblast growth factor 23 and klotho cross talk in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2019; 317: L141–54. DOI: 10.1152/ajplung.00246.2018.
21. Gao W., Yuan C., Zhang J. et al. Klotho expression is reduced in COPD airway epithelial cells: effects on inflammation and oxidant injury. Clin Sci (Lond). 2015; 129: 1011–23.
22. Zhang J., Cao K., Pastor J.V. et al. Alpha-Klotho, a critical protein for lung health, is not expressed in normal lung. FASEB Bio Advances. 2019; 1: 675–87. DOI: 10.1096/fba.2019-00016.
23. Ashley B. et al. Placental uptake and metabolism of 25(OH) vitamin D determine its activity within the fetoplacental unit. eLife. 2022. DOI: 10.7554/eLife.71094.
24. Mandell E., Seedorf G.J., Ryan S. et al. Antenatal endotoxin disrupts lung vitamin D receptor and 25-hydroxyvitamin D 1α-hydroxylase expression in the developing rat. Am J Physiol Lung Cell Mol Physiol. 2015; 309: L1018–26.
25. Hart P.H., Lucas R.M., Walsh J.P. et al. Vitamin D in fetal development: findings from a birth cohort study. Pediatrics. 2015; 135: e167–73.
26. Feng H., Xun P., Pike K. et al. In utero exposure to 25 hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: a meta-analysis of birth cohort studies. J Allergy Clin Immunol. 2017; 139: 1508–17.
27. Augusto A Litonjua, Vincent J Carey, Nancy Laranjo et al. Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction. N Engl J Med. 2020; 382(6): 525–33 DOI: 10.1056/NEJMoa1906137.
28. Журавлева Л.Н., Новикова В.И. Витамин Д и антимикробные пептиды при врожденной пневмонии у недоношенных новорожденных. Иммунопатология, аллергология, инфектология. 2021; 1: 13–9. DOI: 10.14427/jipai.2021.1.13. EDN ASHJTU.
29. Britt RDJ., Faksh A., Vogel E.R. et al. Vitamin D attenuates cytokine-induced remodeling in human fetal airway smooth muscle cells. J Cell Physiol. 2015; 230: 1189–98. DOI: 10.1002/jcp.24953.
30. Zhang J., Cao K., Pastor J.V. et al. Alpha-Klotho, a critical protein for lung health, is not expressed in normal lung. FASEB BioAdvances. 2019; 1: 675–87. DOI: 10.1096/fba.2019-00016.
31. Li P., Xu X., Cao E. et al. Vitamin D deficiency causes defective resistance to Aspergillus fumigates in mice via aggravated and sustained inflammation. PLoS One. 2014; 9: e99805. DOI: 10.1371/journal.pone.0099805.
32. Heulens N., Korf H., Cielen N. et al. Vitamin D deficiency exacerbates COPD-like characteristics in the lungs of cigarette smoke-exposed mice. Respir Res. 2015; 16: 110. DOI: 10.1186/s12931-015.
33. Krick S., Baumlin N., Aller S.P. et al. Klotho inhibits interleukin-8 secretion from cystic fibrosis airway

epithelia. Sci Rep. 2017; 7: 14388. DOI: 10.1038/s41598-017-14811.
34. Barnes J.W., Duncan D., Helton S.et al. Role of fibroblast growth factor 23 and klotho cross talk in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2019; 317: L141–54. DOI: 10.1152/ajplung.00246.2018.
35. Krick S., Grabner A., Baumlin N. et al. Fibroblast growth factor 23 and Klotho contribute to airway inflammation. Eur Respir J. 2018; 52: 1800236. DOI: 10.1183/13993003.00236-2018.
36. Shou-En Wu., Wei-Liang Chen Soluble klotho as an effective biomarker to characterize inflammatory states Ann. Med. 2022; 54(1): 1520–9. DOI: 10.1080/07853890.2022.2077428.
37. Chaeuk Chung, Prashanta Silwal, Insop Kim et al. Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. Immune Netw. 2020; 20(2): e12. English. Published online Feb 11, 2020. https://doi.org/10.4110/in.2020.20.e12.
38. Schrumpf J.A., Amatngalim G.D., Veldkamp J.B. et al. Proinflammatory cytokines impair vitamin D-induced host defense in cultured airway epithelial cells. Am J Respir Cell Mol Biol. 2017; 56: 749–76. DOI: 10.1183/13993003.01009-2017.
39. Heulens N., Korf H., Mathyssen C. et al. 1,25 Dihydroxyvitamin D modulates antibacterial and inflammatory response in human cigarette smoke exposed macrophages. PLoS One. 2016; 11: e0160482. DOI: 10.1371/journal.pone.0160482.
40. Wang Z., Zhang H., Sun X., Ren L. The protective role of vitamin D_3 in a murine model of asthma via the suppression of TGF-β/Smad signaling and activation of the Nrf2/HO-1 pathway. Mol Med Rep. 2016; 14: 2389–96.
41. Ravikumar P., Ye J., Zhang J. et al. Klotho protects against oxidative damage in pulmonary epithelia. Am J Physiol Lung Cell Mol Physiol. 2014; 307: L566–75.
42. Zhang R., Zhao H., Dong H. et al. 1α,25-Dihydroxyvitamin D_3 counteracts the effects of cigarette smoke in airway epithelial cells. Cell Immunol. 2015; 295: 137–14.
43. DiFranco K.M., Mulligan J.K., Sumal A.S., Diamond G. Induction of CFTR gene expression by $1,25(OH)_2$ vitamin D_3, 25OH vitamin D_3, and vitamin D_3 in cultured human airway epithelial cells and in mouse airways. J Steroid Biochem Mol Biol. 2017; 173: 323–32.

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FEATURES OF GASTROINTESTINAL PATHOLOGY INDUCED BY ALLERGY TO COW'S MILK PROTEIN IN PEDIATRIC PRACTICE (LITERATURE REVIEW)

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Abstract. According to statistics from all types of atopy in children, food allergies occupy the first place in terms of prevalence. In turn, cow's milk is a food product that most often acts as an allergen. Not rarely, gastrointestinal diseases become one of the manifestations of allergy to cow's milk protein. Currently, it is customary to distinguish the following clinical forms of gastrointestinal pathology induced by allergy to cow's milk protein: specific IgE-mediated reactions and non-IgE-mediated reactions, as well as their combination — mixed-type reactions. In routine pediatric practice, however, non-IgE-mediated forms still remain poorly recognized. This is due to a variety of factors: a variety of clinical manifestations, the lack of reliable methods of laboratory diagnostics, a non-obvious association with time and a causal relationship with an allergen. The article reflects modern views on the features of the clinical course and diagnosis of gastrointestinal pathology induced by allergy to cow's milk protein.

Key words: *children; esophagitis; gastritis; enterocolitis; proctocolitis; allergy to cow's milk protein.*

ОСОБЕННОСТИ ГАСТРОИНТЕСТИНАЛЬНОЙ ПАТОЛОГИИ, ИНДУЦИРОВАННОЙ АЛЛЕРГИЕЙ К БЕЛКУ КОРОВЬЕГО МОЛОКА, В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. По статистике из всех видов атопий у детей первое место по распространенности занимает пищевая аллергия. В свою очередь коровье молоко — продукт питания, который чаще всего выступает аллергеном. Нередко одним из проявлений аллергии к белку коровьего молока становятся гастроинтестинальные заболевания. В настоящее время принято выделять следующие клинические формы гастроинтестинальной патологии, индуцированной аллергией к белку коровьего молока (БКМ): специфические IgE-опосредованные реакции и не-IgE-опосредованные, а также их сочетание — реакции смешанного типа. Однако в рутинной педиатрической практике не-IgE-опосредованные формы по-прежнему остаются плохо распознаваемыми. Это обусловлено многими факторами: разнообразие клинических проявлений, отсутствие достоверных методов лабораторной диагностики, неочевидная ассоциация со временем

и причинно-следственной связью с аллергеном. В статье отражены современные взгляды на особенности клинического течения и диагностики гастроинтестинальной патологии, индуцированной аллергией к белку коровьего молока.

Ключевые слова: *дети; эзофагит; гастрит; энтероколит; проктоколит; аллергия к белку коровьего молока.*

INTRODUCTION

Over the last years, there has been an increase in gastrointestinal diseases induced by cow's milk protein allergy (CMPA) worldwide as this pathology is highly represented [1, 2]. According to the World Allergy Organization (WAO), cow's milk proteins (CMPs) as well as chicken egg proteins are the most important triggers of food allergy in infants and young children [3]. The use of milk formulas for infant feeding plays an important role in the formation of CMPA. However, exclusively breastfed children may also develop clinical manifestations of CMPA due to the penetration of food proteins into breast milk. CMPs can be found not only in dairy products made of cow's milk, but also in some probiotics, oral polio vaccine, diphtheria-pertussis-tetanus vaccine, and some inhalers used in the treatment of bronchial asthma, such as Fluticasone/Salmeterol or Lanimavir [4].

The first clinical signs of CMPA manifest within the period from 10 days to 10 months of life, 3.5 months on the average. Typically, symptoms appear within the first week after the introduction of products containing CMPs (95% of cases). It has been proven that the use of milk formulas containing CMPs during can the development of the first symptoms in 60% of patients. Various forms of gastrointestinal pathology appear in 32–60% of children, skin manifestations occur in 5–90% of children [5], anaphylactic reaction may develop in 0.8–9% of cases [6, 7].

Currently, it is accepted to distinguish the following variants of CMPs [8]:

1) specific IgE-mediated:
- immediate gastrointestinal hypersensitivity;
- oral allergic syndrome;

2) eosinophilic diseases (mixed IgE and non-IgE-dependent):
- eosinophilic esophagitis;
- eosinophilic gastritis;
- eosinophilic gastroenteritis;
- eosinophilic enterocolitis;

3) non-IgE-mediated reactions:
- food protein-induced enterocolitis syndrome;
- food protein-induced proctocolitis;
- protein-induced protein-losing enteropathy.

The peculiarity of the gastrointestinal form of CMPA manifestation is the diversity of a clinical picture since any part of the gastrointestinal tract (GIT) may be involved in the pathological process [9]. Gastroesophageal reflux (GER), nausea, vomiting, diarrhea, bloody stools, and stabbing pains in the abdominal region may be among the first manifestations of IgE-mediated CMPA. The specific clinical picture and association with the allergen contributes to rapid differentiation of this pathology [10]. However, non-IgE-mediated reaction is also a common pathology and can account for up to 50% of all CMPA cases in pediatric practice. The clinical picture in this form of pathology is varied, and the symptoms usually increase slowly, which can make the diagnosis difficult. It is also characterized by decreased appetite, pale skin, infantile colic, possible development of bleeding from the upper GIT, GER, development of chronic diarrhea or constipation, blood and/or mucus in feces [11]. In the present article, common variants of IgE and non-IgE-mediated reactions of gastrointestinal pathology induced by CMPA are discussed.

ESOPHAGEAL LESIONS

Gastroesophageal reflux. CMPA (often non-IgE-mediated variant) may manifest with GER symptoms such as crying, signs of regurgitation, vomiting and sleep disturbance. It is noted that persistent regurgitation is a common non-specific symptom of CMPA in children. According to the literature, CMPA has been documented in 50% of children with persistent GER. Possible manifestations of CMPA include decreased physical development, diarrhea or rectal bleeding on the background of any symptoms of atopy [12]. Diagnosis of this pathology in pediatric practice is difficult as it requires daily esophageal impedance-pH-metry and endoscopy of the upper GIT [13]. In order to eliminate these symptoms, it is recommended to use formulas based on protein hydrolysate or amino acids, or eliminate products containing CMPs in the diet of a nursing mother for 2–4 weeks [14].

Eosinophilic esophagitis (EoE) is a chronic, slowly progressive immune-mediated disease of the esophagus characterized by marked eosinophilic

inflammation of esophageal mucosa, development of submucosal fibrosis, clinically manifested by swallowing disorders (dysphagia, esophageal obstruction by a food clump, vomiting of swallowed food, etc.) [15]. From the pathophysiological point of view, EoE is a chronic Th2-associated esophageal disease characterized by the development of marked eosinophilic inflammation (more than 15 eosinophils in the field of view on a high-resolution microscope with ×400 magnification) in the esophageal mucosa and submucosal fibrosis, clinically manifested by esophageal dysfunction such as difficulty in eating, vomiting, choking, refusal to eat in children and dysphagia in adolescents and adults.

The nature and severity of complaints may vary depending on the age of a patient and duration of the medical history since EoE is a slowly progressive disease [16, 17]. Children of the first years of life have nonspecific symptoms which include regurgitation, nausea and vomiting during meals, difficulty with swallowing certain foods (seafood, eggs, nuts, etc.), abdominal pain, and physical retardation (rarely). Adolescents' complaints are similar to GER: heartburn, pain behind the sternum, the need to chew food for a long time and wash it down with water. Esophagogastroduodenoscopy (EGDS) in patients with EoE reveals nonspecific signs of active inflammation throughout the esophagus: edema and contact vulnerability of the esophageal mucosa, whitish exudate (eosinophilic microabscesses), longitudinal grooves. In addition to the above mentioned, signs of submucosal fibrosis may be found in adolescents and adult patients: multiple concentric rings ("tracheal" or "cat" esophagus), strictures and narrowings of the esophagus [18].

Histologic study includes examination of biopsy specimens using a high-resolution microscope (×400), staining with hematoxylin and eosin. To obtain correct histologic results, biopsy should be performed in at least 6–8 sections from the distal and mid/proximal esophagus. The biopsy specimen should include the epithelium to its entire depth and the intrinsic mucosal lamina. These recommendations are induced by inflammatory changes in EoE which are focal and equally involve both distal and proximal parts of the esophagus [19].

GASTRIC LESIONS

Isolated gastric involvement in CMPA is rare; however, in some cases, the occurrence of prolonged vomiting may contribute to the development of hemorrhagic gastritis in patients. Endoscopic examination of the upper GIT with biopsy of gastric mucosa is a necessary tool to confirm the diagnosis. The study of such biopsy specimens may show eosinophilic infiltration of the mucosa. The etiologic diagnosis is made in accordance with clinical guidelines for the diagnosis of CMPA. The elimination diet prescribed usually yields positive results with complete spontaneous resolution of symptoms within one week [20].

It should be noted that cow's milk has long been used to alleviate clinical symptoms of peptic ulcer disease or GERD due to its acid-neutralizing features. However, the high calcium and protein content significantly increases hydrochloric acid production by gastric parietal cells. As confirmed by an endoscopic study [21], patients with peptic ulcer disease who followed a dairy-free diet had better ulcer scarring results than those who consumed milk.

LESIONS OF SMALL INTESTINE AND COLON

Exudative or protein-induced protein-losing enteropathy is a rare clinical syndrome involving a loss of serum proteins through the GIT [22]. In infancy, this pathology corresponds to a mixed IgE and non-IgE-immune-mediated food allergy characterized by villous atrophy that leads to enteric protein loss, causing hypoproteinaemia/hypoalbuminaemia, diarrhea, peripheral and cavity edema, and, consequently, malabsorption symptoms. Laboratory diagnosis may show signs of anemic syndrome, eosinophilia, hypoalbuminaemia, increased fecal α1-antitrypsin (α1AT), increased specific IgE, and a positive reaction in the prick-test [23]. The pathogenesis is based on the inability of GIT mucous membranes (not only intestine, but also esophagus and stomach) to retain tissue proteins. Serum protein levels reflect the balance between synthesis, metabolism, and protein loss. Exudative enteropathy is characterized by increased protein loss through the GIT compared to synthesis. Whereas albumins are characterized by a long half-life (20 days), it is hypoalbuminaemia that reflects hypoproteinaemia. Laboratory elevation of fecal α1AT is a marker of protein loss through a digestive system [24]. The diagnosis is based on the effects of the elimination diet prescribed as clinical improvement usually occurs within 3–4 days, however, it may take several weeks for complete elimination of symptoms [25, 26].

Food Protein Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated disease. It manifests in infancy at 1–4 weeks of age, beginning with recurrent prolonged vomiting that occurs approximately in 1–4 hours after a meal. Vomiting is often accompanied by pallor, diarrhea, and lethargy. The delayed acute onset and the absence of cutaneous and respiratory symptoms indicate a systemic reaction of the body which differs from an anaphylactic reaction [18]. The most common causes of this pathology are CMPs, soy and cereals. A pronounced loss of weight and a decreased physical development rate arise with a prolonged chronic course of the disease. FPIES is often misdiagnosed as acute viral gastroenteritis, sepsis, or acute surgical pathology, leading to incorrect therapeutic tactics.

A carefully collected medical history plays a special role in the diagnosis of FPIES. In the vast majority of patients with acute FPIES, a single episode is sufficient to make the diagnosis and identify the syndrome's causative products. If the diagnosis is unclear after careful history taking, an oral provocation test should be used as the gold standard for clarification.

There are major and minor diagnostic criteria which make it possible to suspect the disease [28]. Major criteria: vomiting within 1–4 hours after ingestion and absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria: 1) second (or more) episode of recurrent vomiting after eating the same food; 2) recurrent episodic vomiting in 1–4 hours after ingestion; 3) lethargy with any reaction; 4) pallor with any reaction; 5) need for emergency department admission for any reaction; 6) need for intravenous administration with any reaction; 7) diarrhea in 24 hours (usually 5-10 h); 8) hypotension; 9) hypothermia.

To diagnose FPIES, a patient must have a major criterion and at least three minor criteria presented. In case only one episode of FPIES is noted, a diagnostic oral provocation test should be strongly recommended to confirm the diagnosis, as viral gastroenteritis is common in this age group [29].

Proctocolitis induced by food proteins (eosinophilic proctocolitis, allergic proctocolitis) is a transient and benign manifestation of non-IgE-induced GIT lesions. Protein-induced proctocolitis prevalence remains unknown, however it accounts for 0.16 to 64% among all rectal bleeding in infants [30]. It is more common in breastfed infants (60%) and resolves when the mother eliminates CMPs and soy proteins from her diet [31].

The pathogenesis of proctocolitis induced by food proteins remains inconclusive. The main pathophysiologic mechanism is eosinophilic inflammation: at least 10 eosinophils per field of view are found in biopsy specimens of the colonic mucosa. At the same time, according to C. De Brosse et al. [32], eosinophils (on average 16–20 cells in the field of view) are also detected in healthy children GIT (the control group), especially in the colon.

The main clinical symptom of the disease is diarrhea with blood and, sometimes, mucus in feces. An objective examination of a patien shows no hyperemia and fissures in the perianal area. Some children have colic-like abdominal pain, increased gas and painful defecation. As a rule the volume of feces is small, consequently dehydration does not develop. The pathology does not disturb general condition and development of children [32]. These symptoms may appear in 12 hours after ingestion of a causative allergen and may increase further if the allergen continues to be in daily meals. Adherence to an elimination diet can relieve diarrhea and hematochezia within 2–3 days.

Currently there are no generally recognized standard clinical criteria for diagnosing enterocolitis induced by food proteins. In clinical practice, the diagnosis is made in case the symptoms resolved on the background of the elimination diet and then they have returned after reintroduction of the trigger product. Eosinophilia in peripheral blood occurs in 44% of patients. In rare cases, hypochromic anemia and minor thrombocytosis may be observed in laboratory tests [32].

Endoscopic examination of the upper GIT and histologic diagnosis of biopsy material are necessary for differential diagnosis with other conditions causing rectal bleeding. The histological picture is characterized by colitis with eosinophilic infiltration of the intrinsic lamina and muscular layer of the colonic mucosa (more than 6 eosinophils in the field of view) with the formation of eosinophilic crypt abscesses and erosions [32].

The oral provocation test is the "gold standard" for the diagnosis of proctocolitis induced by food proteins. Re-introduction of the suspected product after 4-8 weeks of elimination may be performed at home and shall be documented in a symptom diary in case visible blood in the feces appear. If there is no blood, a fecal occult blood test is recommended [33].

CONCLUSIONS

Gastrointestinal pathology induced by allergy to cow's milk proteins is common in pediatric practice. Due to the variety of clinical forms and manifestations, the diagnostic search is often difficult and should be primarily based on a thorough collection of a patient's medical history. Disappearance of symptoms and their appearance during a provocative oral test should also alert a physician. A coordinated approach is required among allergists, gastroenterologists and nutritionists, nurses and caregivers since the diagnosis is difficult. Further research on the prevalence, pathophysiology, diagnostic markers, and treatment of this pathology is also needed in order to improve patient care.

ADDITIONAL INFORMATION

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

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REFERENCES

1. Kosenkova T.V., Novikova V.P., Boytsova E.A. Vvedenie. Epidemiologiya pishchevoy allergii. Faktory, vliyayushchie na ee formirovanie. [Introduction. Epidemiology of food allergies. Factors influencing its formation]. V knige: Problemy pishchevoy allergii u detey: mekhanizmy razvitiya, osobennosti techeniya, klinicheskie varianty, podkhody k lecheniyu, dietoterapiya. Moskva; 2022: 13–23. (In Russian).
2. Kosenkova T.V., Novikova V.P., Boytsova E.A. Osnovnye patogeneticheskie mekhanizmy formirovaniya pishchevoy allergii. [The main pathogenetic mechanisms of food allergy formation]. V knige: Problemy pishchevoy allergii u detey: mekhanizmy razvitiya, osobennosti techeniya, klinicheskie varianty, podkhody k lecheniyu, dietoterapiya. Moskva; 2022: 23–7. (In Russian).
3. Fiocchi A., Bognanni A., Brożek J. et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. Allergy Organ J. 2022; 15(1): 100609. DOI: 10.1016/j.waojou.2021.100609.
4. Mastrorilli C., Santoro A., Caffarelli C. Primary Prevention of Allergic Diseases: The Role of Early Exposure to Cow's Milk Formula. Front Pediatr. 2020; 8: 420. DOI: 10.3389/fped.2020.00420.
5. Barinova A.N., Gelezhe K.A., Zamyatina Yu.E. Atopicheskiy dermatit. mezhdistsiplinarnyy podkhod k diagnostike i lecheniyu. [Atopic dermatitis. a multidisciplinary approach to diagnosis and treatment]. Rukovodstvo dlya vrachey. Moskva; 2023. (In Russian).
6. Novikova V.P. Diagnostika allergicheskikh zabolevaniy zhkt v pediatricheskoy praktike. [Diagnosis of allergic diseases of the gastrointestinal tract in pediatric practice]. V sbornike: Izbrannye trudy Obshchestva detskikh gastroenterologov, gepatologov i nutritsiologov "Detskaya gastroenterologiya 2019". Pod obshchey redaktsiey A.I. Khavkina, V.P. Novikovoy, G.V. Volynets. Moskva-Sankt-Peterburg; 2019: 6–32. (In Russian).
7. Kosenkova T.V., Novikova V.P., Gurova M.M. Problemy pishchevoy allergii u detey: mekhanizmy razvitiya, osobennosti techeniya, klinicheskie varianty, podkhody k lecheniyu, dietoterapiya. [Problems of food allergy in children: developmental mechanisms, features of the course, clinical options, treatment approaches, dietary therapy]. Moskva; 2022. (In Russian).
8. Novik G.A., Tkachenko M.A. Gastrointestinal'nye proyavleniya pishchevoy allergii u detey. [Gastrointestinal manifestations of food allergies in children]. Lechashchiy vrach. 2012; 1: 16–25 (In Russian).
9. Gurova M.M. Pishchevaya allergiya i pishchevaya neperenosimost'. [Food allergies and food intolerance]. Children's Medicine of the North-West. 2022; 10(2): 5–21. (In Russian).
10. Gayduk I.M., Koltuntseva I.V., Novikova V.P. i dr. Gastrointestinal'nye proyavleniya pishchevoy allergii u detey: oral'nyy allergicheskiy sindrom.

[Gastrointestinal manifestations of food allergy in children: oral allergic syndrome]. Eksperimental'naya i klinicheskaya gastroenterologiya. 2022; 1(197): 120–9. DOI: 10.31146/1682-8658-ecg-197-1-120-129. (In Russian).
11. Walsh J., Meyer R., Shah N. et al. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations. Br. J. Gen. Pract. 2016; 66: e609–11. DOI: 10.3399/bjgp16X686521.
12. Salvatore S., Agosti M., Baldassarre M.E. et al. Cow's milk allergy or gastroesophageal reflux disease-can we solve the dilemma in infants? Nutrients. 2021; 13. DOI: 10.3390/nu13020297.
13. Rosen R., Vandenplas Y., Singendonk M. et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American society for pediatric gastroenterology, hepatology, and nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J. Pediatr. Gastroenterol Nutr. 2018; 66: 516–54.
14. Martin C.R., Ling P.R., Blackburn G.L. Review of infant feeding: key features of breast milk and infant formula. Nutrients. 2016; 8. DOI: 10.3390/nu8050279.
15. Lucendo A.J., Molina-Infante J., Arias Á. et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017; 5(3): 335–58. DOI: 10.1177/2050640616689525.
16. Steinbach E.C., Hernandez M., Dellon E.S. Eosinophilic esophagitis and the eosinophilic gastrointestinal diseases: approach to diagnosis and management. J. Allergy Clin. Immunol. Pract. 2018; 6(5):1483–95. DOI: 10.1016/j.jaip.2018.06.012.
17. Zamyatina Yu.E. Sovremennye predstavleniya o eozinofil'nom ezofagite. [Modern notions of eosinophilic esophagitis]. V sbornike: Pishchevaya neperenosimost' u detey. Sovremennye aspekty diagnostiki, lecheniya, profilaktiki i dietoterapii. Sbornik trudov II Vserossiyskoy nauchno-prakticheskoy konferentsii. Pod red. V.P. Novikovoy, T.V. Kosenkovoy. 2017: 25–41. (In Russian).
18. Hirano I., Moy N., Heckman M.G. et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013; 62: 489–95. DOI: 10.1136/gutjnl-2011-301817.
19. Straumann A., Katzka D.A. Diagnosis and treatment of eosinophilic esophagitis. Gastroenterology. 2018; 154(2): 346–59. DOI: 10.1053/j.gastro.2017.05.066.
20. Suzuki S., Homma T., Kurokawa M. et al. Eosinophilic gastroenteritis due to cow's milk allergy presenting with acute pancreatitis. Int. Arch. Allergy Immunol. 2012; 158(1): 75–82. DOI: 10.1159/000337782.
21. Kumar N., Kumar A., Broor S.L. et al. Effect of milk on patients with duodenal ulcers. Br Med J (Clin Res Ed). 1986; 293: 666. DOI: 10.1136/bmj.293.6548.666.
22. Braamskamp M.J., Dolman K.M., Tabbers M.M. Clinical Practice Protein-losing enteropathy in children. Eur J Pediatr. 2010; 169: 1179–85. DOI: 10.1007/s00431-010-1235-2.
23. Feketea G., Popp A., Ionescu D.M. et al. Case Report: Food Protein-Induced Protein Losing Enteropathy (FPIPLE) in infancy. Front. Nutr. 2022; 9: 810409. DOI: 10.3389/fnut.2022.810409.
24. Umar S.B., DiBaise J.K. Protein-losing enteropathy: case illustrations and clinical review. Am. J. Gastroenterol. 2010; 105: 43–9. DOI: 10.1038/ajg.2009.561.
25. Grigor'eva K.M., Sinyugina A.I., Novikova V.P. Nutritivnyy status detey, stradayushchikh allergicheskoy enteropatiey. [Nutritional status of children suffering from allergic enteropathy]. University Therapeutic Journal. 2023; 5(1): 122–9. DOI: 10.56871/UTJ.2023.38.66.010. (In Russian).
26. Feuille E., Nowak-Węgrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. Curr Allergy Asthma Rep. 2015; 15.
27. Jarvinen K.M., Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. J. Allergy Clin. Immunol. Pract. 2013; 1(4): 317–22. DOI: 10.1016/j.jaip.2013.04.004.
28. Sicherer S.H. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J. Allergy Clin. Immunol. 2005; 115(1): 149–56. DOI: 10.1016/j.jaci.2004.09.033.
29. Novikova V.P., Pokhlebkina A.A. Enterokoliticheskiy sindrom, indutsirovannyy pishchevymi belkami, v praktike pediatra. [Enterocolytic syndrome induced by dietary proteins in pediatrician practice]. Pediatr. 2019; 10(2): 69–74. DOI: 10.17816/PED10269-74. (In Russian).
30. Leonard S. Non-IgE-mediated Adverse Food Reactions. Curr. Allergy Asthma Rep 2017; 17: 84. DOI: 10.1007/s11882-017-0744-8.
31. Vassilopoulou E., Feketea G., Konstantinou G.N. et al. Food protein-induced allergic proctocolitis: the effect of maternal diet during pregnancy

and breastfeeding in a mediterranean population. Front Nutr. 2022; 9: 843437. DOI: 10.3389/fnut.2022.843437.
32. De Brosse C.W., Case J.W., Putnam P.E. et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. Pediatr Dev Pathol 2006; 9: 210–8. DOI: 10.2350/11-05-0130.1.
33. Caubet J.C., Szajewska H., Shamir R., Nowak-Wegrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. Pediatr Allergy Immunol. 2017; 28: 6–17. DOI: 10.1111/pai.12659.

ЛИТЕРАТУРА

1. Косенкова Т.В., Новикова В.П., Бойцова Е.А. Введение. Эпидемиология пищевой аллергии. Факторы, влияющие на ее формирование. В книге: Проблемы пищевой аллергии у детей: механизмы развития, особенности течения, клинические варианты, подходы к лечению, диетотерапия. М.; 2022: 13–23.
2. Косенкова Т.В., Новикова В.П., Бойцова Е.А. Основные патогенетические механизмы формирования пищевой аллергии. В книге: Проблемы пищевой аллергии у детей: механизмы развития, особенности течения, клинические варианты, подходы к лечению, диетотерапия. М.; 2022: 23–7.
3. Fiocchi A., Bognanni A., Brożek J. et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. Allergy Organ J. 2022; 15(1): 100609. DOI: 10.1016/j.waojou.2021.100609.
4. Mastrorilli C., Santoro A., Caffarelli C. Primary Prevention of Allergic Diseases: The Role of Early Exposure to Cow's Milk Formula. Front Pediatr. 2020; 8: 420. DOI: 10.3389/fped.2020.00420
5. Баринова А.Н., Гележе К.А., Замятина Ю.Е. Атопический дерматит. Междисциплинарный подход к диагностике и лечению. Руководство для врачей. М.; 2023.
6. Новикова В.П. Диагностика аллергических заболеваний ЖКТ в педиатрической практике. В сборнике: Избранные труды Общества детских гастроэнтерологов, гепатологов и нутрициологов «Детская гастроэнтерология 2019». Под общей редакцией А.И. Хавкина, В.П. Новиковой, Г.В. Волынец. М.-СПб.; 2019: 6–32.
7. Косенкова Т.В., Новикова В.П., Гурова М.М. Проблемы пищевой аллергии у детей: механизмы развития, особенности течения, клинические варианты, подходы к лечению, диетотерапия. М.; 2022.
8. Новик Г.А., Ткаченко М.А. Гастроинтестинальные проявления пищевой аллергии у детей. Лечащий врач. 2012; 1: 16–25.
9. Гурова М.М. Пищевая аллергия и пищевая непереносимость. Children's Medicine of the North-West. 2022; 10(2): 5–21.
10. Гайдук И.М., Колтунцева И.В., Новикова В.П. и др. Гастроинтестинальные проявления пищевой аллергии у детей: оральный аллергический синдром. Экспериментальная и клиническая гастроэнтерология. 2022; 1(197): 120–9. DOI: 10.31146/1682-8658-ecg-197-1-120-129.
11. Walsh J., Meyer R., Shah N. et al. Differentiating milk allergy (IgE and non-IgE mediated) from lactose intolerance: understanding the underlying mechanisms and presentations. Br. J. Gen. Pract. 2016; 66: e609–11. DOI: 10.3399/bjgp16X686521.
12. Salvatore S., Agosti M., Baldassarre M.E. et al. Cow's milk allergy or gastroesophageal reflux disease-can we solve the dilemma in infants? Nutrients. 2021; 13. DOI: 10.3390/nu13020297.
13. Rosen R., Vandenplas Y., Singendonk M. et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American society for pediatric gastroenterology, hepatology, and nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J. Pediatr. Gastroenterol Nutr. 2018; 66: 516–54.
14. Martin C.R., Ling P.R., Blackburn G.L. Review of infant feeding: key features of breast milk and infant formula. Nutrients. 2016; 8. DOI: 10.3390/nu8050279.
15. Lucendo A.J., Molina-Infante J., Arias Á. et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017; 5(3): 335–58. DOI: 10.1177/2050640616689525.
16. Steinbach E.C., Hernandez M., Dellon E.S. Eosinophilic esophagitis and the eosinophilic gastrointestinal diseases: approach to diagnosis and management. J.Allergy Clin. Immunol. Pract. 2018; 6(5):1483–95. DOI: 10.1016/j.jaip.2018.06.012.
17. Замятина Ю.Е. Современные представления о эозинофильном эзофагите. В сборнике: Пищевая непереносимость у детей. Современные аспекты диагностики, лечения, профилактики и диетотерапии. Сборник трудов II Всероссийской научно-практической конференции. Под ред. В.П. Новиковой, Т.В. Косенковой. 2017: 25–41.
18. Hirano I., Moy N., Heckman M.G. et al. Endoscopic assessment of the oesophageal features of eosi-

nophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013; 62: 489–95. DOI: 10.1136/gutjnl-2011-301817.
19. Straumann A., Katzka D.A. Diagnosis and treatment of eosinophilic esophagitis. Gastroenterology. 2018; 154(2): 346–59. DOI: 10.1053/j.gastro.2017.05.066.
20. Suzuki S., Homma T., Kurokawa M. et al. Eosinophilic gastroenteritis due to cow's milk allergy presenting with acute pancreatitis. Int. Arch. Allergy Immunol. 2012; 158(1): 75–82. DOI: 10.1159/000337782.
21. Kumar N., Kumar A., Broor S.L. et al. Effect of milk on patients with duodenal ulcers. Br Med J (Clin Res Ed). 1986; 293: 666. DOI: 10.1136/bmj.293.6548.666.
22. Braamskamp M.J., Dolman K.M., Tabbers M.M. Clinical Practice Protein-losing enteropathy in children. Eur J Pediatr. 2010; 169: 1179–85. DOI: 10.1007/s00431-010-1235-2.
23. Feketea G., Popp A., Ionescu D.M. et al. Case Report: Food Protein-Induced Protein Losing Enteropathy (FPIPLE) in infancy. Front. Nutr. 2022; 9: 810409. DOI: 10.3389/fnut.2022.810409.
24. Umar S.B., DiBaise J.K. Protein-losing enteropathy: case illustrations and clinical review. Am. J. Gastroenterol. 2010; 105: 43–9. DOI: 10.1038/ajg.2009.561.
25. Григорьева К.М., Синюгина А.И., Новикова В.П. Нутритивный статус детей, страдающих аллергической энтеропатией. University Therapeutic Journal. 2023; 5(1): 122–9. DOI: 10.56871/UTJ.2023.38.66.010.
26. Feuille E., Nowak-Węgrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. Curr Allergy Asthma Rep. 2015; 15.
27. Jarvinen K.M., Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. J. Allergy Clin. Immunol. Pract. 2013; 1(4): 317–22. DOI: 10.1016/j.jaip.2013.04.004.
28. Sicherer S.H. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J. Allergy Clin. Immunol. 2005; 115(1): 149–56. DOI: 10.1016/j.jaci.2004.09.033.
29. Новикова В.П., Похлебкина А.А. Энтероколитический синдром, индуцированный пищевыми белками, в практике педиатра. Педиатр. 2019; 10(2): 69–74. DOI: 10.17816/PED10269-74.
30. Leonard S. Non-IgE-mediated Adverse Food Reactions. Curr. Allergy Asthma Rep 2017; 17: 84. DOI: 10.1007/s11882-017-0744-8.
31. Vassilopoulou E., Feketea G., Konstantinou G.N. et al. Food protein-induced allergic proctocolitis: the effect of maternal diet during pregnancy and breastfeeding in a mediterranean population. Front Nutr. 2022; 9: 843437. DOI: 10.3389/fnut.2022.843437.
32. De Brosse C.W., Case J.W., Putnam P.E. et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. Pediatr Dev Pathol 2006; 9: 210–8. DOI: 10.2350/11-05-0130.1.
33. Caubet J.C., Szajewska H., Shamir R., Nowak-Wegrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. Pediatr Allergy Immunol. 2017; 28: 6–17. DOI: 10.1111/pai.12659.

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ANALYSIS OF THE STRUCTURE OF CASES OF EMERGENCY HOSPITALIZATION IN CHILDREN WITH TRAUMATIC INJURIES

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Abstract. Identifying the relationship between age, the scene of the accident and the nature of the damage makes it possible to develop measures to reduce the frequency of injuries. The cases of emergency hospitalization of children with injuries to the St. Petersburg State Medical University clinic in 2021 were analyzed. Fractures and bruises were a common cause of hospitalization of children aged 1–17 years. Boys aged 1–3 years and 13–17 years were more often hospitalized with injuries. In the group of 13–17 years, fractures of the wrist and hand bones were more often observed. In children 1–3 years old, bruises received in everyday life were more common. At the age 4–7 years, fractures of the forearm bones prevailed, most often received in everyday life. In the group of 8 years and older, there was a high frequency of fractures of the bones of the hand and forearm, received on the street or during sports.

Key words*: children; traumatism; prevention.*

АНАЛИЗ СТРУКТУРЫ СЛУЧАЕВ ЭКСТРЕННОЙ ГОСПИТАЛИЗАЦИИ У ДЕТЕЙ С ТРАВМАТИЧЕСКИМИ ПОВРЕЖДЕНИЯМИ

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Резюме. Выявление взаимосвязи между возрастом, местом происшествия и характером повреждения дает возможность разработки мероприятий, позволяющих снизить частоту травматизма. Проанализированы случаи экстренной госпитализации детей с травмами в клинику СПбГПМУ в 2021 году. Частой причиной госпитализации детей 1–17 лет явились переломы и ушибы. С травмами чаще госпитализировались мальчики в возрасте 1–3 и 13–17 лет. В группе 13–17 лет чаще наблюдались переломы костей запястья и кисти. У детей 1–3 лет чаще встречались ушибы, полученные в быту. В возрасте 4–7 лет преобладали переломы костей предплечья, чаще полученные в быту. В группе от 8 лет и старше отмечалась высокая частота переломов костей кисти и предплечья, полученных на улице или при занятиях спортом.

Ключевые слова: *дети; травматизм; профилактика.*

INTRODUCTION

Child injuries are a topical medical and social problem in paediatrics. The high rate of injuries has remained the same over the past 10 years [1]. The prevention of child injuries and the creation of a safe environment for child health are priorities for health institutions worldwide [2].

The incidence of injuries in children in Saint Petersburg is significantly higher among boys in the age range of 14–17 [3]. The trend of high fre-

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quency of injuries among adolescent boys is also observed in other regions of Russia (Khabarovsk, Tyumen, Orenburg) [4–6].

The high incidence of injuries in childhood is considered by many authors to be a result of a certain "traumatic behavior" which may be due to a certain type of upbringing [7, 8]. Also important are the age factor (psychomotor development) and the presence of behavioral disorders (high incidence of injuries in children with attention deficit hyperactivity syndrome (ADHD) and attention deficit disorder) [9].

Injury during physical education classes and sports classes is more frequent among boys, with a peak in the age range of 7–10 years with decreases in older age [5].

Among the total number of injuries in children in Saint Petersburg in the period 2015–2017, the most frequent were superficial injuries (40%), dislocation and sprained joints (15%), and wounds (11%). Of all injuries recorded, upper limb fractures were 13.3%, lower limb fractures were 5.4%, vertebral and torso fractures were 1.4%, and thermal and chemical burns were 2.1% [10].

The incidence of injuries in children in Saint Petersburg in 2018 was significantly higher than the average for Russia (106.4‰ in children and 176.7‰ in adolescents). 93.3% of patients received first aid and outpatient treatment in the traumatological cabinet and traumatological units of children's polyclinics, in traumatological units of adult`s polyclinics. About 8% were sent to the hospital [11].

THE PURPOSE OF THE STUDY

Study of the structure of traumatic injuries in children admitted to the hospital after trauma, bypassing the outpatient care unit. On the basis of data analysis, develop basic guidelines for the prevention of child injuries.

MATERIALS AND METHODS

1,072 medical records of children aged 1 to 17 were analyzed. All children were hospitalized with acute injuries without going through the outpatient phase of trauma care. The study included 687 boys and 385 girls. All children were divided into age groups: 1–3 years (n=137), 4–7 years (n=198), 8–12 years (n=336), and 13–17 years (n=401).

The obtained results are statistically processed using Microsoft Excel and reliability criterion.

RESULTS AND DISCUSSION

Among the hospitalized children in all groups, they were predominantly boys: children under the age of 3 and 13–17 (Fig. 1).

All injuries were subdivided into fractures, dislocations, open wounds, bruises, sprains, and ligaments. Bruises and fractures were discovered among all the injuries. Bruises dominated in 37.2% of cases in the group of children aged 1–3; in other age groups, fractures predominated (Fig. 2).

The localization of injuries in the structure was dominated by the upper extremities (n=779), lower extremities (n=231), spine (n=20), superficial head injuries (n=17), abdominal injuries (n=11), back injuries (soft tissue) (n=9), thorax (n = 3), and external genitals (n=2).

In the case of injuries in everyday life (n=473), the main reasons were: pinning the fingers with doors (more often among children under 3 years) in 33.4% of cases; a fall on the slippery floor in 28%; accidental blows by distal limbs (with a fist on the wall, on the table, etc., more often among

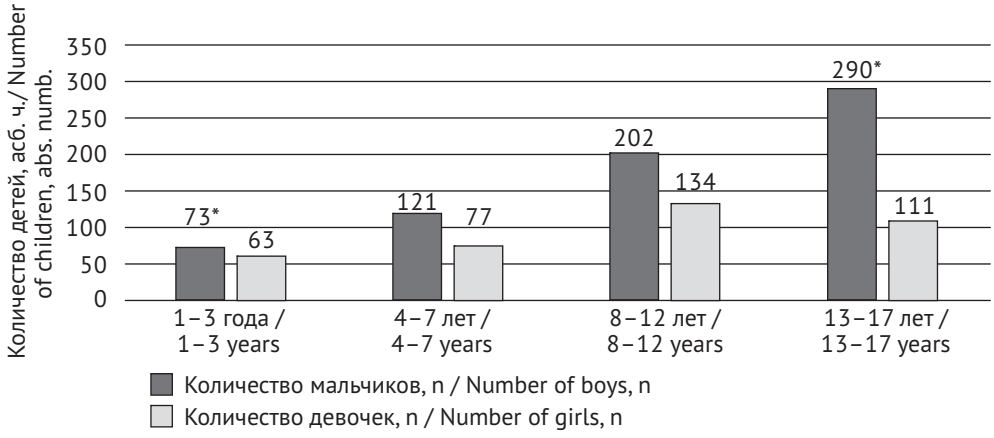

Fig. 1. The number of cases of emergency hospitalization with injuries in children in 2021 year (*p ⩽0,05)

Рис. 1. Количество случаев экстренной госпитализации с травмами у детей за 2021 год (*p ⩽0,05)

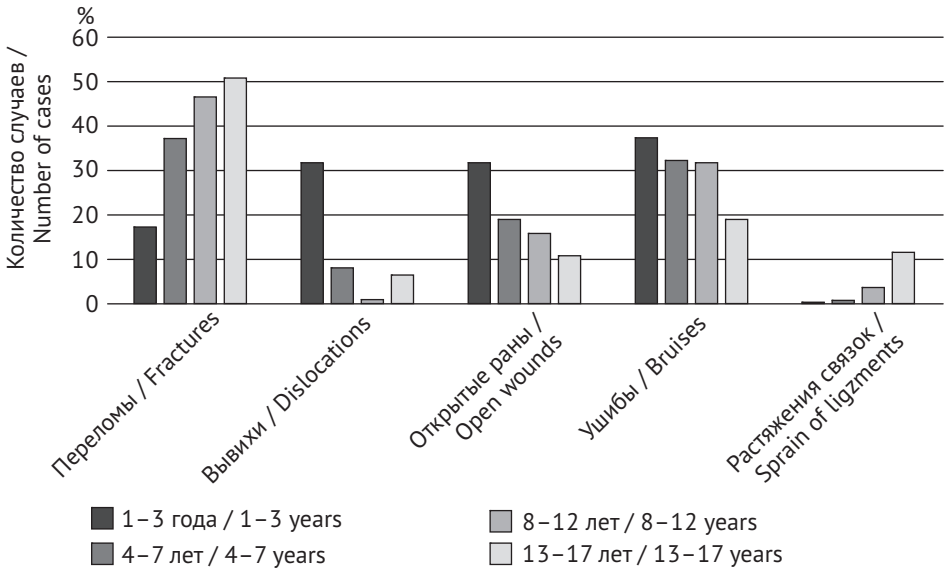

Fig. 2. The structure of traumatic injuries in children hospitalized on an emergency in 2021

Рис. 2. Структура травматических повреждений у детей, госпитализированных в экстренном порядке в 2021 году

Table 1. Characteristics of localization of traumatic injuries in boys and girls

Таблица 1. Характеристика локализаций травматических повреждений у мальчиков и девочек

Травма / Injury	Количество мальчиков, n=687/ Number of boys, n=687		Количество девочек, n=385 / Number of girls, n=385		p
Вывихи / Dislocations	48	7,0%	44	11,4%	≤0,05
Открытые раны / Open wounds	97	14,1%	57	14,8%	>0,05
Переломы / Fractures	306	44,5%	153	39,7%	>0,05
Ушибы / Bruises	196	28,5%	104	27,0%	>0,05
Растяжения, разрывы связок / Sprains, ligament tears	40	5,9%	27	7,0%	>0,05

children from 4 years and older) in 20.9%; and injury to sharp household items (knives, sharp corners of furniture, etc.) in 17.7% of cases.

In the case of injuries on the street and in public places (n=297), the main reasons were: outdoor sports equipment (gym, swings, horizontal bar, trampoline) in 67.6% of cases; falling from a bike, scooter, etc. in 20.2% of cases; hitting the ball in 7.4% of cases; and sharp force wounds in 4.7% of cases.

Injuries sustained in sports sections (n=251) as a result of unsuccessful falls were observed in 67.7% of cases, in combat techniques (gripping, blows, etc.) — in 18.3% of cases, and in other exercises — in 14.0% of cases.

In kindergarten (n=12) injuries are obtained as a result of pinning the fingers with doors (n=10), unsuccessful falls on the floor (n=2). In school (n=39) in physical education classes (n=26) — as a result of falls when running, folding of limbs, kick the ball, as well as other lessons. School breaks, as a result of conflicts with peers or pranks (n=13).

Children aged 1–3 and 4–7 are injured most often in everyday life. Children aged 8–12 are mainly injured at home, on the street, and in public places. Children in the older age group were more likely to be injured on the street, in public places, and in sports.

Differences were found in the types of traumatic injuries in boys and girls.

The most frequent injuries leading to emergency hospitalization were fractures at 42.8% (n=459), bruises at 28.0% (n=300), open wounds at 14.3% (n=154), dislocation at 8.6% (n= 92), and sprains and ligament ruptures at 6.3% (n=67).

When analyzing the number of all fractures in the age groups, two groups showed a predominance: children 8–12 (46.7%) and 12–17 (50.9%), with no reliable difference between the groups (p >0.05). There was a clear difference in the

number of fractures between groups of children aged 1–3 (17.5%), 4–7 (46.5%), and 12–17 (50.9%) (p≤0.05).

Among all fractures (n=459) the most common localizations were the bones of the wrist and fingers — 48.6% (n=223), the bones of the forearm — 19.8% (n=91) and the shoulder — 8.9% (n=41) cases.

Fractures of the bones of the wrist and hand were most common and with a high degree of certainty (p ≤0.05) in the 13–17 age group — 58.3%, and fractures of the bones of the forearm in the 8–12 age group — 26.1%.

Less commonly found were fractures of the tibia (n=36), clavicles (n=29), feet (n=24), fractures of the vertebrae (n=11) and femurs (n=4).

When comparing the number of cases of fractures in boys and girls, the most frequent localization was fractures of the bones of the wrist and fingers: 52.3% of girls and 46.7% of boys (p >0.05). Localization of fractures of the forearm was reliably more prevalent in the group of boys (22.5%) than in girls (14.4% of cases) (p ≤0.05).

Bruises accounted for 28.0% (n=300) of all injuries hospitalized on an emergency basis. The most frequent localization of bruises was injuries to the wrists and fingers — in 54.7% (n=164), forearms — in 10.3% (n=31), feet — in 9.0% (n=27) cases.

It was found that the number of bruises predominated in children from 1 to 3 years of age — 37.2% of all injuries in this age group, which was reliably higher than the incidence in children from 12 to 17 years of age — in 19.2% of cases (p ≤0.05). Children aged 4–7, 32.8%, had bruises, and children aged 8–12, 31.8 % (p >0.05).

Among the bruises, contusions that required emergency hospitalization of the upper limbs prevailed mainly on the wrists and fingers.

The analysis of the number of cases of localized bruises in the wrist and hand showed a predominance in the age group of children 1–3 with 72.5% of cases, and in the group 4–7 years with the frequency of wrist and hand 63,0%, which is different from the 8–12 age group with a frequency of 43.9% and 12–17 years with a frequency of 50.6% (p ≤0.05).

In the age group 8–12 years in 35.7% of cases (n=107) localized bruises, namely: contusion of the femur (n=3), external genitalia (n=2), and soft tissue of the head (n=1). That was not observed in other age groups.

The most frequent localization of injuries in girls admitted for emergency treatment for bruises (n=104): wrist and hand of 57.7% (n=60) and forearm of 13.4% (n=14); for boys (n=196) wrist and hand of 53.0% (n=104) and forearm regions in 8.7% (n=17) cases (p >0.05).

Open wounds accounted for 14.3% (n=154) of all emergency hospitalizations. The most frequent localization was in the area of the wrist and fingers: 57.4% (n=90); in the area of the foot: 11.0% (n=17) and in the head: 10.4% (n=16) cases.

In the studied age groups, of all emergency hospitalizations for injuries, there was a predominance of open-wound children (4–7 years old) in 19.2% of cases, which was more reliable than in the 13–17 year-old group (p≤0.05). In the group of children 1–3 years old, the open wounds amounted to 12.4%; in the group 8–12 years old, 16.0% (p >0.05).

Between the open wounds in the wrist and hand, there was no reliable difference in the frequency of cases between the groups.

In the 8–12 age group there were localizations of open wounds namely knee (n=3), thorax (n=1), shoulder (n=1). That were wounds not observed in other age groups.

In girls admitted to the hospital on an emergency basis with open wounds, the most frequent localization wounds were wrist and hands: 47.4% (n=27); in boys, wounds of this localization were 64.9% (n=63) cases (p ≤0.05). Fewer injuries were found in girls in the tibia region — 15.8% n=9), and in boys in the foot area 12.3% (n=12).

Dislocations accounted for 8.6% (n=92) of all emergency hospitalization cases and had the most frequent localization in the area of the joints of the forearm — 67.4% (n=62), the patella: 14.1% (n=13) and the fingers: 8.7% (n=8).

Among all cases of dislocation, it was most common in the group of children 1–3 years of age — 32.1%. In the other age groups, the frequency was much lower: in the group of 4–7 years 8.6%, 8-12 years — 1.2%, and 12–17 years — 6.7% (p≤0.05).

Dislocations in the joints of the forearm (radial and elbow) were the reason for hospitalization in the 1–3 age group and accounted for 100% (n=44) of cases.

Among girls admitted to the hospital on an emergency basis due to dislocations, the most frequent localization dislocations were in the joints of the forearm (radius and ulna) — 81.8% (n=36) — and in boys (n=48) — in 54.2% (n=26) cases (p ≤0.05).

Sprains and ligament ruptures accounted for 6.3% (n=67) of all emergency hospitalizations. The localization of ligament sprains corresponded to: wrist and hand — 29% (n=20), ankle — 26.9% (n=18), knee — 23.9% (n=16), neck — 8.9% (n=6), foot joints — 4.5% (n=3), hip joint – 3.0% (n=2), front abdominal muscles — 1.4% (n=1) of cases.

When comparing the incidence of ligament strain in the groups, it was found most frequently in the 13–17 age group — 12.0%, while in the 1–3 age group — 0.7%, 3–7 years — 2.0%, 8–12 years — 4.2 %.

Among girls hospitalized for ligament sprains (n=27), the most frequent localization was in the area of the wrist and hand — 33.3% (n=9), in boys — 59.7% (n=40), the area of the knee — 40.0% (n=17).

CONCLUSIONS

The most common causes of emergency hospitalization among all injuries in children were fractures (42.8%) and bruises (28.0%).

Comparing the frequency and localization of injuries in boys and girls, it was found that boys were reliably more likely to have fractured forearm bones — 22.5%, while girls were 14.4%; open wrist and hand wounds in boys were 64,9%, in girls they were 47.4%. In the analysis of the frequency and localization of dislocations, the group of girls was reliably more frequent — 81.8%, and boys 54.2%. The significant prevalence of dislocation in girls may be related to hormonal status affecting connective-joint function.

In the age analysis structure, children mostly required hospitalization in the age groups 8–12 years — 31.3% and 13–17 years — in 37.4% of cases. Reliably more frequent fractures occurred in the 4–7 age group — in 37.4% of cases, mainly due to fractures of the bones of the forearm. In the 12–17 age group, the fracture rate was 50.9%, mainly due to the localization of the wrist and fingers.

Bruises were more likely to cause hospitalization in children in the 1–3 age group — in 37.2% of cases, with predominant localization in the wrist and hand — in 72.5% of cases.

Dislocations were more often the reason for hospitalization of children aged 1–3 — in 32.1% of cases, with predominant localization in the joints of the forearm (radius and elbow).

Open wounds were more likely to cause hospitalization of children in the 4–7 age group in 19.2% of cases, with the predominant localization of wounds in the wrist and hand — 50% of all injuries in this age group.

Interviews with parents by pediatricians explaining the nature of injuries at each age will reduce the incidence of child injuries.

Young children are more likely to be injured in the form of dislocated wrists and bruises, in everyday life in the use of doors. It is also possible to get injured by children when adults treat a child incorrectly (pull the hand, hang by the wrists during play, etc.). The use of special devices to prevent the complete closing of doors, as well as to explain to parents the rules of treatment and play with the child, given the weakness of the musculoskeletal system in children of this age, will reduce the frequency of injuries.

In the 4 to 7-year-old age range, when the child's own motor activity expands, fractures of the bones of the forearm and open wounds of the hand, forearm with the careless use of sharp objects and fractures predominated among the injuries. The preventive measure for this age period is the control of parents during active play of children and the use of traumatic objects (scissors, knives, etc.).

In the age groups of children aged 8 and over, mainly among boys, there is a high incidence of fractures of the bones of the hand and forearm. These injuries are most often inflicted on a child on the street or in sports. Possible causes of trauma in boys include behaviors with a high level of aggression. The prevention of injurious behavior includes conversations and control when using outdoor fitness equipment, such as bicycles and scooters. It is necessary not only to explain to the child the consequences of such behavior but also to educate the child in his own example of safe behavior in sports and active games. In addition, there is a need for more careful monitoring of sports activities and classes with the participation of not only coaches but also parents.

Knowledge of the structure and mechanism of child injuries will make it possible to develop comprehensive preventive programs. Use them program both at the outpatient level and in educational and sports institutions.

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 pub-

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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.

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

REFERENCES

1. Grechuxin I.V., Kul`kov V.N., Fomichev V.V. Analiz zabolevaemosti detej vsledstvie travm, otravlenij i boleznej kostno-my`shechnoj sistemy` po danny`m oficial`noj statistiki. [Analysis of children's morbidity due to injuries, poisonings and diseases of the musculoskeletal system according to official statistics]. Medicina. 2019; 7(2): 24–39. (In Russian).
2. Sethi, Dinesh, Towner, Elizabeth, Vincenten, Joanne, Segui Gomez, Maria & Racioppi, Francesca. (2009). Doklad o profilaktike detskogo travmatizma v Evrope. [Report on child injury prevention in Europe]. Vsemirnaya organizaciya zdravooxraneniya. Evropejskoe regional`noe byuro. URL: https://iris.who.int/handle/10665/341342 (date of access: 03.01.2024).
3. Solov`eva K.S., Zaletina A.V. Travmatizm detskogo naseleniya Sankt-Peterburga. Ortopediya, travmatologiya i vosstanovitel`naya xirurgiya detskogo vozrasta. [Injuries among children in St. Petersburg]. 2017; 3. URL: https://cyberleninka.ru/article/n/travmatizm-detskogo-naseleniya-sankt-peterburga (date of access: 20.09.2023). (In Russian).
4. Marega L.A., Senkevich O.A., Lemeshhenko O.V., Kaplieva O.V. Prichina i struktura detskogo travmatizma v g. Xabarovske. [Cause and structure of child injuries in Khabarovsk]. Dal`nevostochny`j medicinskij zhurnal. 2019; 4. URL: https://cyberleninka.ru/article/n/prichiny-i-struktura-detskogo-travmatizma-v-g-habarovske (date of access: 20.09.2023). (In Russian).
5. Kolunin E.T., Prokop`ev N.Ya., Baranxin O.V. Profilaktika detskogo travmatizma na zanyatiyax fizicheskoj kul`turoj i sportom. [Prevention of childhood injuries in physical education and sports]. Sovremenny`e problemy fizicheskoj kul`tury i sporta. 2020:140-145. (In Russian).
6. Golovko O.V., Pavlenko T.N. Kliniko-statisticheskij analiz travmatizma sredi detskogo i podrostkovogo naseleniya g. Orenburga. [Clinical and statistical analysis of injuries among children and adolescents in Orenburg]. ZNiSO. 2017;10(295). URL: https://cyberleninka.ru/article/n/kliniko-statisticheskiy-analiz-travmatizma-sredi-detskogo-i-podrostkovogo-naseleniya-g-orenburga (date of access: 20.09.2023). (In Russian).
7. Shhetinin S.A. Analiz chastoty` i posledstvij travmatizma v Rossii. [Analysis of the frequency and consequences of injuries in Russia]. Sovremenny`e problemy` nauki i obrazovaniya. 2015;2-1:48. (In Russian).
8. Ruiz-Goikoetxea M., Cortese S., Aznarez-Sanado M. et al. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews. 2018;84:63–71. DOI: 10.1016/j.neubiorev.2017.11.007
9. Karamy`sheva M.B. Faktory, sposobstvuyushhie vozniknoveniyu povtornyx neprednamerennyx fizicheskix travm u detej v vozraste 5–10 let. [Factors contributing to the occurrence of repeated unintentional physical injuries in children aged 5–10 years]. Molodye issledovateli za ustojchivoe razvitie. Sbornik statej V Mezhdunarodnoj nauchno-prakticheskoj konferencii. Petrozavodsk, 2023: 239-250. (In Russian).
10. Baindurashvili A.G., Vissarionov S.V., Solovyeva K.S., Zaletina A.V. Detskij travmatizm i okazanie specializirovannoj pomoshhi detyam v megapolise. [Child injury and provision of specialized care to children in the metropolis]. Rossijskij vestnik detskoj hirurgii, anesteziologii i reanimatologii. 2018;8(2):16-23. DOI: 10.30946/2219-4061-2018-8-2-16-23. (In Russian).
11. Baindurashvili A.G. i dr. Detskij travmatizm v Sankt-Peterburge i okazanie travmatologicheskoj pomoshhi detyam v 2016–2018 godax. [Child in-

jury in St. Petersburg and provision of trauma care to children in 2016–2018]. Ezhegodnaya nauchno-prakticheskaya konferenciya, posvyashhennaya aktual`ny`m voprosam travmatologii i ortopedii detskogo vozrasta "Turnerovskie chteniya", 8–9 oktyabrya 2020 goda. Sbornik statej. Gl. red. A.G. Baindurashvili; red. S.V. Vissarionov, V.M. Kenis, A.V. Zaletina, A.V. Ovechkina, K.S. Solovyeva. Sankt-Peterburg; 2020: 31-39.

ЛИТЕРАТУРА

1. Гречухин И.В., Кульков В.Н., Фомичев В.В. Анализ заболеваемости детей вследствие травм, отравлений и болезней костно-мышечной системы по данным официальной статистики. Медицина. 2019; 7 (2): 24–39.
2. Sethi, Dinesh, Towner, Elizabeth, Vincenten, Joanne, Segui Gomez, Maria & Racioppi, Francesca. (2009). Доклад о профилактике детского травматизма в Европе. Всемирная организация здравоохранения. Европейское региональное бюро. URL: https://iris.who.int/handle/10665/341342 (дата обращения: 03.01.2024).
3. Соловьева К.С., Залетина А.В. Травматизм детского населения Санкт-Петербурга. Ортопедия, травматология и восстановительная хирургия детского возраста. 2017; 3. URL: https://cyberleninka.ru/article/n/travmatizm-detskogo-naseleniya-sankt-peterburga (дата обращения: 20.09.2023).
4. Марега Л.А., Сенькевич О.А., Лемещенко О.В., Каплиева О.В. Причина и структура детского травматизма в г. Хабаровске. Дальневосточный медицинский журнал. 2019. № 4. URL: https://cyberleninka.ru/article/n/prichiny-i-struktura-detskogo-travmatizma-v-g-habarovske (дата обращения: 20.09.2023).
5. Колунин Е.Т., Прокопьев Н.Я., Баранхин О.В. Профилактика детского травматизма на занятиях физической культурой и спортом. Современные проблемы физической культуры и спорта. 2020: 140–145.
6. Головко О.В., Павленко Т.Н. Клинико-статистический анализ травматизма среди детского и подросткового населения г. Оренбурга. ЗНиСО. 2017; 10 (295). URL: https://cyberleninka.ru/article/n/kliniko-statisticheskiy-analiz-travmatizma-sredi-detskogo-i-podrostkovogo-naseleniya-g-orenburga (дата обращения: 20.09.2023).
7. Щетинин С.А. Анализ частоты и последствий травматизма в России. Современные проблемы науки и образования. 2015; 2-1: 48.
8. Ruiz-Goikoetxea M., Cortese S., Aznarez-Sanado M. et al. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews. 2018;84:63-71. DOI: 10.1016/j.neubiorev.2017.11.007.
9. Карамышева М.Б. Факторы, способствующие возникновению повторных непреднамеренных физических травм у детей в возрасте 5–10 лет. Молодые исследователи за устойчивое развитие. Сборник статей V Международной научно-практической конференции. Петрозаводск; 2023: 239–250.
10. Баиндурашвили А.Г., Виссарионов С.В., Соловьева К.С., Залетина А.В. Детский травматизм и оказание специализированной помощи детям в мегаполисе. Российский вестник детской хирургии, анестезиологии и реаниматологии, 2018; 8(2): 16-23. DOI: 10.30946/2219-4061-2018-8-2-16-23.
11. Баиндурашвили А.Г. и др. Детский травматизм в Санкт-Петербурге и оказание травматологической помощи детям в 2016–2018 годах. Ежегодная научно-практическая конференция, посвященная актуальным вопросам травматологии и ортопедии детского возраста «Турнеровские чтения», 8–9 октября 2020 года. Сборник статей. Гл. ред. А. Г. Баиндурашвили; ред. С.В. Виссарионов, В.М. Кенис, А.В. Залетина, А.В. Овечкина, К.С. Соловьева. СПб.; 2020: 31–39.

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ANALYSIS OF EATING BEHAVIOR AND PHYSICAL ACTIVITY OF FIRST-YEAR MEDICAL UNIVERSITY STUDENTS

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Abstract. The beginning of student life is associated with significant changes in lifestyle, which can contribute to the emergence/intensification of eating disorders and changes in physical activity, which in turn can be a starting factor for a disadaptation to the learning process. To determine the type of eating behavior and level of physical activity, we studied interview data from 146 first-year medical students. The analysis of nutritional status was carried out based on the mass-growth index. Food behavior was tested using the EAT-26 and DEBQ questionnaires and motor activity was tested using IPAQ, MAQ23+ questionnaires. We discovered that a significant number of first-year university students have abnormalities in nutritional status, insufficient — 18.7%, overweight — 16.4% of students. Abnormal nutritional symptoms related to cognitive, behavioral, and emotional domains are present in one-third of female students. Restrictive nutrition was considered a risk factor by 26.6%. Approximately 80% of female students did not get enough physical activity and 60% displayed hypodynamy symptoms. The peculiarities of food behavior and motor activity, combined with the individual characteristics of female students, may be a marker of disadaptation to the educational process in the university.

Key words: *eating behavior; physical activity; students; nutritional status.*

АНАЛИЗ ПИЩЕВОГО ПОВЕДЕНИЯ И ФИЗИЧЕСКОЙ АКТИВНОСТИ ПЕРВОКУРСНИКОВ МЕДИЦИНСКОГО УНИВЕРСИТЕТА

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Резюме. Начало студенческой жизни сопряжено со значительными изменениями образа жизни, которые могут способствовать возникновению / усилению расстройств пищевого поведения и изменению двигательной активности, что, в свою очередь, может быть пусковым фактором дезадаптации к учебному процессу. С целью определить тип пищевого поведения и уровень физической активности мы изучили данные интервьюирования 146 студенток первого курса медицинского университета. Проведен анализ нутритивного статуса по массо-ростовому индексу; тестирование пищевого поведения по опросникам EAT-26 и DEBQ; двигательной активности — по опросникам IPAQ, ОДА23+. Нами выявлено, что у значительной

части студенток первого курса университета имеются отклонения в нутритивном статусе, обусловленные в равной степени как недостаточным (18,7%), так и избыточным весом (16,4%). Треть студенток демонстрируют абнормальные симптомы пищевого поведения, относящиеся к когнитивной, поведенческой и эмоциональной сферам. В группу риска ограничительного питания вошли 26,6%. У 80% студенток уровень физической активности недостаточен, признаки гиподинамии демонстрировали 60% респондентов. Выявленные особенности пищевого поведения и двигательной активности в сочетании с индивидуальными характеристиками личности студенток могут быть маркером дезадаптации к учебному процессу в вузе.

Ключевые слова: *пищевое поведение; физическая активность; студенты; нутритивный статус.*

INTRODUCTION

According to the World Health Organization (WHO) concept, of the many exogenous factors influencing the formation and maintenance of human health, the most significant are nutritional characteristics and level of physical activity. Malnutrition, both insufficient and overweight, is recognized as an important health and social problem. According to the WHO, nearly 1.9 billion adults are overweight or obese, while 462 million are underweight [15]. In 2016, the United Nations General Assembly declared a decade of unprecedented struggle against all forms of malnutrition. It approved the "Global Monitoring Framework for Nutrition. Operational guidance to track progress towards the 2025 goals" [14]. According to domestic research, for the period from 2000 to 2018, The share of increased obesity among young people has increased fourfold, and the frequency of obesity has increased 2.7 times [6, 8]. The prevalence of overweight ranges from 3.9 to 29.1%; obesity ranges from 1.2 to 25.3% in the younger age groups of the country, depending on gender and living conditions [2, 3, 16, 17]. The prevalence of body mass deficiency is less well understood.

Eating behavior (EB) is understood as a lifestyle component that incorporates a nutrition stereotype and behaviors. There is a focus on the image of one's own body and the activities that shape that image. The formation of EB is influenced by a number of factors: social, economic, ethnocultural, personal, educational environment, etc. [8, 13]. The emotional sphere plays an important role in the formation of EB. Hunger satisfaction is associated with a sense of comfort, quality of life, and security. With the beginning of student life, the daily routine, the type of nutrition, and the volume of educational and psycho-emotional load change significantly. A number of studies have shown that people who are frequently subjected to stressors experience changes in EB, both through overeating and fasting [4, 11, 12]. At the same time, dietary habits can be considered a predictor of desadaptation to the education at the university [1, 5].

THE PURPOSE OF THE STUDIES

To determine the types of eating behaviors and levels of physical activity in medical university students at the beginning of their professional training.

MATHERIAL AND METHODS

The study involved 146 female students aged 17 to 20 (average age M=19.5; SD=1.4), studying in the first year of the Saint Petersburg State Paediatric Medical University, on the basis of voluntariness and confidentiality. The study used the method of conducting a sociological survey by means of a questionnaire. A survey form was compiled on the basis of the Internet platform "Google Forms". The questionnaire included anthropometric data (weight and height) and questions to identify eating behaviors and levels of physical activity.

The nutritional status of a person is usually evaluated by the mass-growth index Ketle (body mass index, or BMI) in global practice, the value of which is determined by dividing the body mass (kg) by the growth square (m^2). The weight-to-height ratio is considered optimal at a BMI between 18.5 and 24.9. At BMI, less than 18.5 were underweight; 25.0 to 29.9 were overweight; and those above 30 were obese [6, 15]. The screening evaluation of the EB was performed using the EAT-26 and DEBQ tests. The EAT-26 scale (Eating Attitudes Test) is the most popular tool that allows you to determine the nature of eating behavior and the propensity for eating disorders. In the case of people with a high probability of nutritional deprivation, advice from subject matter experts should be recommended [9]. The Dutch Eating Behavior Questionnaire (Dutch Eating Behavior Questionnaire) is a simple and validated

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tool that provides a diagnosis of emotional, external, and restrictive types of EB disorder [5, 7]. The following tests were used to determine the level of physical activity (PA): a questionnaire that determines the PA level depending on the motivation for lifestyle changes. The international questionnaire IPAQ (International Questionnaire on Physical Activity) allows for the analysis of the PA for the last week to allocate persons with hypodynamy. The MAQ23+ questionnaire provides a dynamic assessment of the level and degree of PA [10]. Statistica 10.0 was used for quantitative data processing.

DISCUSSION OF THE RESULTS

The nutritional status assessment was based on the weights and height indicated by the girls in the questionnaire. The harmonious weight-to-height ratio was 64.9% of female students; weight deficiency was 18.7% of respondents. Overweight was found in 12.8% of female students; obesity was reported by 3.6% of female students, with BMI corresponding to morbidity obesity in two. In general, the nutritional status of students corresponds to the general trend of physical development of youth in the country [2, 6, 16].

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The EAT-26 test assesses three factors related to eating: 1) Dieting (dieting, avoiding eating calories, tending to lose weight); 2) Bulimia and Food Preoccupation (bulimia symptoms and concern with food-related thoughts); 3) Oral Control (self-control of eating behavior and perceived intention of others to make the respondent eat more). For the quantitative estimation of the respondents' answers, we used the ranking from 0 ("never") to 5 points ("always"), followed by recoding according to the requirements of the original version, where the answers "never", "rarely" and "sometimes" are assigned 0 points, "often" is 1 point, "usually" is 2 points, and "always" is 3 points. This is how all points were evaluated, except for the 26th, which was evaluated in reverse order.

The EAT-26 (≥20) was taken as the critical value to place respondents at risk for EB disorder. The dietary risk group was 26.6%; bulimia and food anxiety 25.1%; and food control 23.2%. In our study, the number of respondents with a propensity for violating EBs was higher than the number of female students in Moscow, Ryazan, and Arkhangelsk (13.5%) who took part in similar testing [9].

In the Dutch DEBQ questionnaire, the first ten questions concern restrictive EB, which is characterized by deliberate efforts to achieve or maintain desired weight through self-restraint in nutrition. The average for this category of people is 2.4 points. If the result is greater and the respondent limits himself to eating, anorexia may be a threat. In our study, the average was 2.86 [min=1.0; max=4.5], indicating an increased prevalence of restrictive EB among female students.

Questions from the 11th through the 23rd address emotional eating behavior, where the desire to eat arises in response to negative emotional states. The nine points on the scale refer to certain emotional states such as irritation, depression (confusion), anger, anticipation of an unpleasant event, anxiety (tension, anxiety), feeling that everything is bad, fright, disappointment, and emotional shock (disorder); and four points refer to states with mixed emotions (when there is nothing to do, a state of boredom or excitement). The average score in this group is no higher than 1.8 points; at a higher score, there is a tendency to "eat" stress. Our participants had an average of 2.36 [min — 1.0; max — 4.8], which indicates an increased frequency of violation of the EB of emotional etiology.

In other questions, DEBQ analyzes the externality of behavior (dietary temptation). In this form of violation of EBs in people, the desire to eat is not stimulated by a real sense of hunger. The appearance of food, its smell, texture, or watching others eat stimulates a sense of hunger. The average score is 2.7 points. If the figure is higher, then there is a difficulty in keeping from appetizing food. In our study, the average was 3.33 [min —1.7; max —4.0]. According to a number of authors, 7.2 to 13.1% of the population of economically developed countries regularly overeat; over the past 30 years, the prevalence of overeating has increased by a factor of 6, with a consequent increase in obesity [1, 5, 13].

A survey of students on their level of physical activity based on motivation showed that 80.5%

of girls try to increase their physical activity. Intensive or moderate PA is performed three times a week and more in the last six months by 12.9% of respondents. However, the remaining girls (6.6%) do not participate in sports and do not plan to increase the PA in the near future.

The IPAQ International Questionnaire identifies people with hypodynamy, which occurs when muscle contraction is reduced. Hypodynamy is indicated by a total of less than 21 points during testing. We measured the frequency of physical activity for 7 days and the time spent on moderate, high-intensity PA in 5 sections: work, movement, housework, leisure, and sitting. Of the girls, 63.6% had normal PA; 12.1% had borderline PA; and 24.3% had hypodynamy. According to MAQ23+ testing, most respondents had moderate levels of physical activity (63.9%). High (5.5%) and very high PA levels (0.7%) were less common than low (29.9%).

CONCLUSION

We have found that a large proportion of female first-year students at the university have abnormalities in nutritional status due to being both insufficient and overweight. The high incidence of physical abnormalities in girls may be related to low physical activity and eating disorders. One-third of female students exhibit abnormal nutritional symptoms related to cognitive, behavioral, and emotional domains. The level of physical activity of female students is insufficient, at 80%. The signs of hypodynamy were demonstrated by 60% of respondents. Among the factors contributing to eating disorders, along with a high level of intellectual and psychoemotional stress during the period of study at the university, special attention should be paid to the individual characteristics of the student's personality.

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 there 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.

REFERENCES

1. Andrievskaya S.V., Karnickaya A.I. Pishchevoe povedenie i irracional'nye ustanovki molodyozhi. [Eating behavior and irrational attitudes of young people]. Aspirant. 2021; 6(63): 25–9. (In Russian).
2. Gritsinskaya V.L., Novikova V.P., Khavkin A.I. K voprosu ob epidemiologii ozhireniya u detey i podrostkov (sistematicheskiy obzor i meta-analiz nauchnykh publikatsiy za 15-letniy period). [On the issue of the epidemiology of obesity in children and adolescents (a systematic review and meta-analysis of scientific publications over a 15-year period)]. Voprosy prakticheskoy pediatrii. 2022; 17(2): 126–35. (In Russian).
3. Gricinskaya V.L., Gubernatorova T.Yu., Permyakova E.S., Havkin A.I. Skriningovaya ocenka nutritivnogo statusa shkol'nikov, prozhivayushchih v razlichnyh regionah Rossijskoj Federacii. [Assessment of nutritional status of schoolchildren residing in different regions of the Russian Federation]. Voprosy prakticheskoj pediatrii. 2020; 15(1): 30–4. DOI: 10.20953/1817-7646-2020-1-30-34. (In Russian).
4. Zavaruhin N.E., Bezuglyj T.A., Torkaj N.A. i dr. Pishchevoe povedenie studentov Yuzhno-Ural'skogo medicinskogo universiteta. [Eating behavior of students of South Ural Medical University]. Nauchnoe obozrenie. Medicinskie nauki. 2022; 3: 36–41. (In Russian).
5. Zaharova E.V. Issledovanie uchebnogo stressa u studentov medicinskogo universiteta. [Study of educational stress among medical university stu-

dents]. Molodoj uchenyj. 2018; 46(232): 251–2. (In Russian).
6. Zimina S.N., Negasheva M.A., Sineva I.M. Izmeneniya indeksa massy tela i povyshennogo zhirootlozheniya moskovskoj molodyozhi v 2000–2018 godah. [Changes in body mass index and increased fat deposition among Moscow youth in 2000–2018]. Gigiena i sanitariya. 2021; 4: 347–57. (In Russian).
7. Lisovskii O.V., Gostimskii A.V., Karpatskii I.V. i dr. Perspektivy distancionnogo obucheniya pri formirovanii professional'nyh kompetencij v medicinskom vuze. [Prospects for distance learning in the formation of professional competencies in a medical university]. Virtual'nye tekhnologii v medicine. 2020; 3(25): 101–2. DOI: 10.46594/2687-0037_2020_3_1235. (In Russian).
8. Mengist G.A., Savvina N.V., Grzhibovskij A.M. i dr. Nutritivnyj status i pishchevoe povedenie studentov universitetov: sistematicheskij obzor. Nutritional status and eating behavior among university students: a systematic review. [Social'nye aspekty zdorov'ya naseleniya]. 2022; 68(5): 11. DOI: 10.21045/2071-5021-2022-68-5-11. (In Russian).
9. Meshkova T.A., Mitina O.V., Shelygin K.V. i dr. Test pishchevyh ustanovok (EAT-26): ocenka psihometricheskih harakteristik i faktornoj struktury na neklinicheskoj vyborke 876 studentok. [Eating Attitudes Test (EAT-26): assessment of psychometric properties and factor structure in a non-clinical sample of 876 female students]. [Elektronnyj resurs]. Klinicheskaya i special'naya psihologiya. 2023; 12(1): 66–103. DOI: 10.17759/cpse.2023120104. (In Russian).
10. Prohorov N.I., Shashina E.A., Makarova V.V., Matveev A.A. Izuchenie pokazatelej dvigatel'noj aktivnosti studentov medicinskogo universiteta. [The studying of physical activity indices in students of medical university]. Gigiena i sanitariya. 2020; 99(8): 816–21. DOI: 10.47470/0016-9900-2020-99-8-816-821. (In Russian).
11. Terekhova A.A., Fedotov N.D., Yamshchikova T.V. Pishchevoe povedenie studentov medicinskogo vuza. [Eating behavior of medical students]. Modern Science. 2021; 4-2: 129–33. (In Russian).
12. Shukshina I.V., Ivanchikov M.A., Samsonova E.A. i dr. Pishchevoe povedenie studentov v period adaptacii v VUZe. [Eating behavior of students during the period of adaptation to university]. Obrazovatel'nyj process. 2019; 6(17): 19–24. (In Russian).
13. Burton A.L., Abbott M.J. Processes and pathways to binge eating: Development of an integrated cognitive and behavioural model of binge eating. J. Eat. Disord. 2019; 7: 18.
14. Global Nutrition Monitoring Framework: operational guidance for tracking progress in meeting targets for 2025. World Health Organization. Geneva. 2018.
15. Global Nutrition Report. 2016. From Promise to Impact: Ending Malnutrition by 2030. World Health Organization. Geneva. 2016.
16. Gritsinskaya V.L., Novikova V.P., Gurova M.M. Prevalence of obesity among schoolchildren in St. Petersburg. Archives of Disease in Childhood. 2019; 104; S3: A366. DOI: 10.1136/archdischild-2019-epa.866.
17. Mitchison D., Touyz S., Gonzalez-Chica D.A. et al. How abnormal is binge eating? 18-Year time trends in population prevalence and burden. Acta Psychiatr. Scand. 2017; 136: 147–55.

ЛИТЕРАТУРА

1. Андриевская С.В., Карницкая А.И. Пищевое поведение и иррациональные установки молодежи. Аспирант. 2021; 6(63): 25–9.
2. Грицинская В.Л., Новикова В.П., Хавкин А.И. К вопросу об эпидемиологии ожирения у детей и подростков (систематический обзор и метаанализ научных публикаций за 15-летний период). Вопросы практической педиатрии. 2022; 17(2): 126–35. DOI: 10.20953/1817-7646-2022-2-126-135.
3. Грицинская В.Л., Губернаторова Т.Ю., Пермякова Е.С., Хавкин А.И. Скрининговая оценка нутритивного статуса школьников, проживающих в различных регионах Российской Федерации. Вопросы практической педиатрии. 2020; 15(1): 30–4. DOI: 10.20953/1817-7646-2020-1-30-34.
4. Заварухин Н.Е., Безуглый Т.А., Торкай Н.А. и др. Пищевое поведение студентов Южно-Уральского медицинского университета. Научное обозрение. Медицинские науки. 2022; 3: 36–41.
5. Захарова Е.В. Исследование учебного стресса у студентов медицинского университета. Молодой ученый. 2018; 46(232): 251–2.
6. Зимина С.Н., Негашева М.А., Синева И.М. Изменения индекса массы тела и повышенного жироотложения московской молодёжи в 2000–2018 годах. Гигиена и санитария. 2021; 4: 347–57.
7. Лисовский О.В., Гостимский А.В., Карпатский И.В. и др. Перспективы дистанционного обучения при формировании профессиональных компетенций в медицинском вузе. Виртуальные технологии в медицине. 2020; 3 (25): 101–2. DOI: 10.46594/2687-0037_2020_3_1235.

8. Менгист Г.А., Саввина Н.В., Гржибовский А.М. и др. Нутритивный статус и пищевое поведение студентов университетов: систематический обзор. Социальные аспекты здоровья населения. 2022; 68(5): 11. DOI: 10.21045/2071-5021-2022-68-5-11.
9. Мешкова Т.А., Митина О.В., Шелыгин К.В. и др. Тест пищевых установок (EAT-26): оценка психометрических характеристик и факторной структуры на неклинической выборке 876 студенток. [Электронный ресурс]. Клиническая и специальная психология. 2023; 12(1): 66–103. DOI: 10.17759/cpse.2023120104.
10. Прохоров Н.И., Шашина Е.А., Макарова В.В., Матвеев А.А. Изучение показателей двигательной активности студентов медицинского университета. Гигиена и санитария. 2020; 99(8): 816–21. DOI: 10.47470/0016-9900-2020-99-8-816-821.
11. Терехова А.А., Федотов Н.Д., Ямщикова Т.В. Пищевое поведение студентов медицинского вуза. Modern Science. 2021; 4-2: 129–33.
12. Шукшина И.В., Иванчиков М.А., Самсонова Е.А. и др. Пищевое поведение студентов в период адаптации в вузе. Образовательный процесс. 2019; 6(17): 19–24.
13. Burton A.L., Abbott M.J. Processes and pathways to binge eating: Development of an integrated cognitive and behavioural model of binge eating. J. Eat. Disord. 2019; 7: 18.
14. Global Nutrition Monitoring Framework: operational guidance for tracking progress in meeting targets for 2025. World Health Organization. Geneva. 2018.
15. Global Nutrition Report.2016. From Promise to Impact: Ending Malnutrition by 2030.World Health Organization. Geneva. 2016.
16. Gritsinskaya V.L., Novikova V.P., Gurova M.M. Prevalence of obesity among schoolchildren in St. Petersburg. Archives of Disease in Childhood. 2019; 104; S3: A366. DOI: 10.1136/archdischild-2019-epa.866.
17. Mitchison D., Touyz S., Gonzalez-Chica D.A. et al. How abnormal is binge eating? 18-Year time trends in population prevalence and burden. Acta Psychiatr. Scand. 2017; 136: 147–55.

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MEDICAL, SOCIAL AND PSYCHOLOGICAL FEATURES OF PATIENTS WITH PULMONARY TUBERCULOSIS AND IN ITS COMBINATION WITH HIV INFECTION

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Abstract. Tuberculosis remains one of the significant health problems today, and is among the leading causes of death among infectious diseases. The number of patients with HIV infection is increasing annually in the world, and the number of people with co-infection with HIV and tuberculosis is increasing accordingly. TB patients and in combination with HIV infection still face stigma from others, making their long-term treatment even more psychotrauming. Among patients with tuberculosis, men of working age, who have secondary and secondary special education, official work and family, are active smokers. They strive to maintain their professional status and actively continue to work, despite the disease, which is typical for patients with an ergopathic type of attitude to the disease. A group of patients with HIV infection is also represented by males, but younger, who do not have official work and families who actively use psychoactive substances, and who were in the past, in places of imprisonment. These patients, as a rule, are characterized by an anosognosic type of attitude to the disease with the expectation of condemnation and prejudice from others. Knowledge of the medical and psychological characteristics of patients with tuberculosis and in combination with HIV infection will allow us to expand our understanding of these groups of patients and accordingly build work with them with their further treatment.

Key words: *tuberculosis; HIV infection; EndTB; portrait of a patient with tuberculosis; medical and social features of patients; psychological features of patients with tuberculosis; copying strategy; type of attitude to the disease of patients with tuberculosis; quality of life of patients with tuberculosis.*

МЕДИКО-СОЦИАЛЬНЫЕ И ПСИХОЛОГИЧЕСКИЕ ОСОБЕННОСТИ БОЛЬНЫХ ТУБЕРКУЛЕЗОМ ЛЕГКИХ И В СОЧЕТАНИИ С ВИЧ-ИНФЕКЦИЕЙ

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Резюме. Туберкулез и сегодня остается одной из значимых проблем здравоохранения и входит в число основных причин смерти среди инфекционных заболеваний. Ежегодно в мире нарастает количество

больных с ВИЧ-инфекцией, а соответственно, увеличивается число лиц с коинфекцией ВИЧ и туберкулез. Больные туберкулезом и сочетанной ВИЧ-инфекцией до сих пор сталкиваются со стигматизацией со стороны окружающих, что делает их длительное лечение еще более психотравмирующим. Среди больных туберкулезом преобладают мужчины трудоспособного возраста, имеющие среднее и среднее специальное образование, официальную работу и семью, являющиеся активными курильщиками. Они стремятся сохранить свой профессиональный статус и активно продолжают работать, несмотря на болезнь, что свойственно для больных с эргопатическим типом отношения к болезни. Группа больных с ВИЧ-инфекцией представлена так же лицами мужского пола, но более молодого возраста, которые не имеют официальной работы и семьи, активно употребляют психоактивные вещества, находились в прошлом в местах лишения свободы. Для этих больных, как правило, характерен анозогнозический тип отношения к болезни, ожидание осуждения со стороны окружающих и наличия у них определенных предубеждений. Знание медико-психологических особенностей больных туберкулезом и сочетанной ВИЧ-инфекцией позволит расширить наше представление об этих группах больных и соответствующим образом построить работу с ними при их дальнейшем лечении.

Ключевые слова: *туберкулез; ВИЧ-инфекция; EndTB; портрет больного туберкулезом; медико-социальные особенности больных; психологические особенности больных туберкулезом; копинг-стратегия; тип отношения к болезни больных туберкулезом; качество жизни больных туберкулезом.*

INTRODUCTION

Tuberculosis and HIV infection are two interrelated and complex problems that pose serious threats to public health in the modern world. The increase in HIV worldwide leads to an increase in tuberculosis associated with HIV. Despite the many global efforts of the World Health Organization (WHO) to combat tuberculosis and HIV infection, these diseases remain one of the leading causes of death worldwide [1].

In 2014, WHO developed the EndTB program, which aims to reduce global tuberculosis morbidity and mortality by 2035. It includes many measures, such as the development of new diagnostic tests and drugs, the introduction of shorter courses of treatment for patients with drug-resistant mycobacteria, and increasing the availability of public health care. The program defines benchmarks for 2020: a reduction in morbidity of 20% and a reduction in mortality of 35%. An 80% reduction in morbidity and a 90% reduction in mortality by 2035. Over time, we have seen that these targets cannot be met. In 2021, the world's morbidity rate fell by 10% and mortality decreased by only 5.9% [1–4].

In 2021, 10.6 million people in the world contracted tuberculosis, and 1.6 million died, with 187.000 of them suffering from HIV-related infections. The combination of tuberculosis and HIV infection significantly worsened the prognosis of the favorable course and outcomes of the disease and the quality of life of these patients. Both diseases are mutually burdensome. Tuberculosis is one of the leading causes of death among people living with HIV. The HIV infection increases the risk of developing tuberculosis by a factor of 20 to 30 compared to uninfected people [1, 5–7].

Tuberculosis patients, including those with HIV infection, often face not only physical but also emotional difficulties. This is related to the manifestation of these diseases and possibly the side effects of drugs. These patients also often face social exclusion and stigmatization. There are associated societal myths and prejudices about these diseases, which in turn can lead to discrimination and exclusion. All this can cause psychological trauma, lead to the development of depressive disorders and anxiety, and further complicate their treatment. It is really important to educate not only the sick but also their surroundings, including relatives, to overcome this stigmatization and raise their awareness of their diseases. Daily work with TB patients and HIV co-infection requires an integrated approach, studying the social and psychological aspects of their lives in modern conditions [8–10].

THE PURPOSE OF THE STUDY

Identification of medical, social, and psychological characteristics of patients with pulmonary tuberculosis and combined HIV infection.

MATERIAL AND METHODS

30 people participated in the pilot study. The first group (G-1) consisted of 16 patients with pulmonary tuberculosis. The second group (G-2) included 14 patients with pulmonary tuberculosis associated with HIV. The study was carried out at the Department of Socially Significant Infections and Phthisiysopulmonology PSPBGMU. I.P. Pavlov

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of the Ministry of Health of Russia and its clinical bases.

The evaluation of health and social characteristics was based on such criteria as gender, age, education, working status, living conditions, marital status, the presence of related diseases and harmful habits, and also previous imprisonment.

For psychological assessment of personality, such methods as the method of diagnosis of types of attitudes toward the disease, the questionnaire of the structure of psychological protection, and the questionnaire used by R. Lazarus and S. Folkman to study Koping strategies were used. The statistical processing of the research materials was carried out using the SPSS 23 application.

RESULTS

Both tuberculosis patients and tuberculosis patients with HIV infection were predominantly male: 56.2% (n=9) and 78.6% (n=11), respectively ($p < 0.05$). Patients in the G-1 group were mostly between 21 and 50 years of age, accounting for 68.8% of all cases (n=11). Among patients in the G-2 group, 64.5% (n=9) were in the age range of 21 to 40 years ($p < 0.05$). As we can see, the patients of these two groups constitute the main labor and fertility cohort of our society.

In estimating the level of education, it was found that 68.8% (n=11) and 64.3% (n=9), respectively ($p < 0.05$), predominate in both groups of patients. Among tuberculosis patients (G-1), 62.5% (n=10) are in formal employment at the time of disease. 42.9% (n=6) of HIV-infected patients in formal employment (G-2) were not officially employed, and 21.4% (n = 4) live off relatives and friends ($p < 0.05$).

An assessment of living conditions showed that among tuberculosis patients (G-1), 62.5% (n=10) lived in a separate apartment. Among pulmonary tuberculosis patients with HIV (G-2), 42.9% (n=6) lived in a communal flat or dormitory ($p < 0.05$).

Of patients with tuberculosis (G-1), 37.2% (n=6) were married at the beginning of treatment. Among those with tuberculosis combined with HIV (G-2), 42.9% (n=6) lived with their parents or were single ($p < 0.05$).

Smoking accounted for 87.5% (n=14), and 37.5% (n=6) abused alcohol ($p < 0.05$). The harmful habits of patients in the second group differed, and in 92.9% of cases (n=13), these patients were active users of psychoactive substances ($p < 0.05$).

The associated pathology in these patients also differs. In tuberculosis patients, chronic obstructive pulmonary disease was detected in 50% of cases (n=8), usually against the background of chronic tobacco intoxication. Among patients in the second group, in addition to HIV infection, 85.7% (n=12) were also diagnosed with viral hepatitis. 71.4% (n=11) of patients suffered from behavioral disorders due to the consumption of psychoactive substances ($p < 0.05$).

In the past, 18.8% (n=3) of G-1 patients had previous imprisonment, while in G-2 patients the figure was significantly higher, at 78.6% (n=11) ($p < 0.05$).

The psychological status assessment showed that the two groups had different attitudes towards the disease. It was found that 37.5% (n=6) of patients with tuberculosis ($p < 0.05$) have an ergopathic attitude toward the disease. The psychotype of these patients was characterized by a very responsible attitude toward treatment. They sought to continue their work and maintain their professional status. Among TB patients combined with HIV (G-2), anozognosis was prevalent in 42.9% (n=6) of cases. There is a strong rejection and neglect of the disease and its consequences ($p < 0.05$). Often, these patients do not follow the advice of the attending physician and violate the treatment regime.

In conditions of illness, all people apply different types of psychological protection, both adaptive and non-adaptive. The study found that "projection" was the type most commonly identified among non-adaptive patients in both groups. It occurred in 50% (n=8) and 71.4% (n=11) of cases, respectively ($p < 0.05$). The main characteristics of patients of this type were prejudice and suspicion toward others. They exaggerated the external danger and often expected a negative attitude towards themselves. Both groups also defined psychological protection as "consumption." It is characterized by relieving stress through the abuse of alcohol, tobacco, psychoactive substances, and/or food. This protection is more pronounced in HIV-infected patients, appears to be the use of psychoactive substances, and is 57.1% (n=8). In tuberculosis patients, it was characterized by smoking and amounted to 47%. (n=7) ($p < 0.05$).

Of the adaptive psychological defenses in both groups, "affiliation" dominated: 56.3% (n=9) in the group G-1 and 42.9% (n=6) in the group G-2 ($p < 0.05$).

The tuberculosis process is a stressor for most patients. So patients from both groups apply dif-

ferent behavioral responses, or so-called coping strategies. They are designed to adapt to the situation and overcome stress. An evaluation of studies of coping strategies showed that 87.5% (n=14) of G-1 patients and 64.3% (n=9) of G-2 patients use the copying strategy "seeking information about their disease" ($p < 0.05$). This data tells us that patients are not sufficiently aware of it, its treatment, and its prognosis. They are constantly searching for information from various sources, such as the Internet, brochures, non-medical articles, or from other patients.

CONCLUSION

On the basis of the conducted research, we have found that the medical, social, and psychological characteristics of the patients in both groups are different. For example, men between the ages of 21 and 50 with specialized high school education or specialized secondary education and formal employment predominate among tuberculosis patients. They live in a separate apartment with their family. Among the associated pathologies, most are diagnosed with "chronic obstructive pulmonary disease", which is often associated with high tobacco consumption. These patients are characterized by ergopathic attitudes toward the disease using protective mechanisms such as projection and attachment.

Patients with a combined HIV infection are characterized by a predominance of men of working age and younger. They have high school education and specialized secondary education; they may be unemployed, live alone, or have parents. They suffer from viral hepatitis and behavioral disorders related to the use of psychoactive substances and have been imprisoned in the past. They tend to have anosognostic attitudes toward disease and defensive reactions such as projection and consumption.

The current medical, social, and psychological profile of tuberculosis patients and HIV infection is complex and multidimensional. They need to require an integrated approach and the active participation of both patients and health professionals, including medical psychologists, in their further treatment and management.

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 there 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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REFERENCES

1. Vsemirnaya organizaciya zdravoohraneniya. Global'nyj doklad VOZ o bor'be s tuberkulezom 2022. [WHO Global Tuberculosis Report 2022]. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022. (In Russian).
2. Kolomiec V M., Medvedeva N.N. Kliniko-psihologicheskie osobennosti u bol'nyh razlichnymi formami tuberkuleza legkih. [Clinical and psychological features in patients with various forms of pulmonary tuberculosis]. Tuberkulez i social'no-znachimye zabolevaniya. 2019; 1: 79–80. (In Russian).
3. Ivanova D.A. Rodina O.V., Borisov S.E. Faktory riska nezhelatel'nyh reakcij pri realizacii rezhimov etiotropnogo lecheniya tuberkuleza s vklyucheniem novyh preparatov. [Risk factors for adverse reactions during the implementation of etiotropic treatment regimens for tuberculosis with the inclusion of new drugs]. Tuberkulez i social'no-znachimye zabolevaniya. 2021; 1: 65–6. (In Russian).
4. Vasil'eva E.B., Lozovskaya M.E., Klochkova L.V. i dr. Epidemiologicheskie aspekty tuberkuleza u detej,

bol'nyh VICH-infekciej. [Epidemiological aspects of tuberculosis in children with HIV infection]. Tuberkulez i bolezni legkih. 2020; 98(9): 33–8. (In Russian).
5. Kazennyj B.Ya. Kiseleva Yu.Yu., Kir'yanova E.V. Neposredstvennye i otdalennye rezul'taty lecheniya bol'nyh s koinfekciej VICH/tuberkulez. [Immediate and long-term results of treatment of patients with HIV/tuberculosis co-infection] Tuberkulez i social'no-znachimye zabolevaniya. 2018; 3: 68–9. (In Russian).
6. Mordyk A.V., Udalova T.Yu., Puzyreva L.V. i dr. Sravnenie lichnostnyh osobennostej vpervye vyyavlennyh bol'nyh infil'trativnym tuberkulezom legkih i s sochetannoj infekciej VICH/tuberkulez. [Comparison of personal characteristics of newly diagnosed patients with infiltrative pulmonary tuberculosis and those with co-infection with HIV/ tuberculosis]. Sibirskoe medicinskoe obozrenie. 2015; 2(92). (In Russian).
7. Brazhenko O.N., Brazhenko N.A., CHujkova A.G. i dr. Iskhod tuberkuleza legkih u bol'nyh VICH-infekciej pri kompleksnom lechenii s aktivaciej zashchitnyh sistem organizma. [Outcome of pulmonary tuberculosis in patients with HIV infection during complex treatment with activation of the body's defense systems]. Tuberkulez i bolezni legkih. 2015; 5: 49–50. (In Russian).
8. Strel'cov V.V., Zolotova N.V., Baranova G.B. i dr. Osobennosti okazaniya psihologicheskoj pomoshchi bol'nym tuberkulezom legkih v faze intensivnoj himioterapii (v usloviyah stacionara). [Features of providing psychological assistance to patients with pulmonary tuberculosis in the phase of intensive chemotherapy (in a hospital setting)]. Tuberkulez i bolezni legkih. 2014; (2): 22–7. (In Russian).
9. Borodulina E.V. Social'nyj portret pacienta s vpervye vyyavlennym tuberkulezom. Nauka i inovaciya v medicine. 2019; 4(2): 43–7. (In Russian).
10. Ohtyarkina V.V., Novoselov P.N. Mediko-social'naya harakteristika pacientov s sochetaniem tuberkuleza i VICH-infekcii. [Medical and social characteristics of patients with a combination of tuberculosis and HIV infection]. Problemy social'noj gigieny, zdravoohraneniya i istorii mediciny. 2012. (In Russian).

ЛИТЕРАТУРА

1. Всемирная организация здравоохранения. Глобальный доклад ВОЗ о борьбе с туберкулезом 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.
2. Коломиец В.М., Медведева Н.Н. Клинико-психологические особенности у больных различными формами туберкулеза легких. Туберкулез и социально-значимые заболевания. 2019; 1: 79–80.
3. Иванова Д.А., Родина О.В., Борисов С.Е. Факторы риска нежелательных реакций при реализации режимов этиотропного лечения туберкулеза с включением новых препаратов. Туберкулез и социально-значимые заболевания. 2021; 1: 65–6.
4. Васильева Е.Б., Лозовская М.Э., Клочкова Л.В. и др. Эпидемиологические аспекты туберкулеза у детей, больных ВИЧ-инфекцией. Туберкулез и болезни легких. 2020; 98(9): 33–8.
5. Казенный Б.Я., Киселева Ю.Ю., Кирьянова Е.В. Непосредственные и отдаленные результаты лечения больных с коинфекцией ВИЧ/туберкулез. Туберкулез и социально-значимые заболевания. 2018; 3: 68–9.
6. Мордык А.В., Удалова Т.Ю., Пузырева Л.В. и др. Сравнение личностных особенностей впервые выявленных больных инфильтративным туберкулезом легких и с сочетанной инфекцией ВИЧ/туберкулез. Сибирское медицинское обозрение. 2015; 2(92).
7. Браженко О.Н., Браженко Н.А., Чуйкова А.Г. и др. Исход туберкулеза легких у больных ВИЧ-инфекцией при комплексном лечении с активацией защитных систем организма. Туберкулез и болезни легких. 2015; 5: 49–50.
8. Стрельцов В.В., Золотова Н.В., Баранова Г.Б. и др. Особенности оказания психологической помощи больным туберкулезом легких в фазе интенсивной химиотерапии (в условиях стационара). Туберкулез и болезни легких. 2014; 2: 22–7.
9. Бородулина Э.В. Социальный портрет пациента с впервые выявленным туберкулезом. Наука и иновация в медицине. 2019; 4(2): 43–7.
10. Охтяркина В.В., Новоселов П.Н. Медико-социальная характеристика пациентов с сочетанием туберкулеза и ВИЧ-инфекции. Проблемы социальной гигиены, здравоохранения и истории медицины. 2012.

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MEDICAL SOVEREIGNTY AND WAYS TO ACHIEVE IT ON THE EXAMPLE OF MINIMALLY INVASIVE GASTROSTOMY

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Abstract. *Introduction.* Medical sovereignty from imported consumables is an important component of State sovereignty. *The purpose of the article* is to propose ways to achieve medical sovereignty on the example of minimally invasive gastrostomy. *Materials and methods.* As part of the dissertation work, a theoretical study of the problem, a series of in vitro and in vivo experiments on laboratory animals, and a clinical study were conducted. *Results.* Original devices have been developed and experimentally tested, which together make up a specialized tube for percutaneous endoscopic gastrostomy. An original technology of minimally invasive gastrostomy is proposed – minimal gastrostomy through minilaparotomy, which reduces dependence on imported consumables. *Conclusions*. The presented original developments will not only make it possible to organize import substitution, but also exert informational pressure on foreign manufacturers to preserve imports.

Key words: *medical sovereignty; minimally invasive gastrostomy; import substitution; domestic developments.*

МЕДИЦИНСКИЙ СУВЕРЕНИТЕТ И ПУТИ ЕГО ДОСТИЖЕНИЯ НА ПРИМЕРЕ МАЛОИНВАЗИВНОЙ ГАСТРОСТОМИИ

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Резюме. *Введение.* Медицинский суверенитет от импортных расходных материалов является важной составляющей государственного суверенитета. *Цель статьи* — предложить пути достижения медицинского суверенитета на примере малоинвазивной гастростомии. *Материалы и методы.* В рамках диссертационной работы проведено теоретическое изучение проблемы, серия экспериментов *in vitro* и *in vivo* на лабораторных животных, клиническое исследование. *Результаты*. Разработаны и апробованы в эксперименте оригинальные приспособления, составляющие в совокупности специализированную трубку для чрескожной эндоскопической гастростомии. Предложена оригинальная технология малоинвазивной гастростомии — минимальная гастростомия через мини-лапаротомию, снижающая зависимость от импортных расходных материалов. *Выводы.* Представленные оригинальные разработки не только позволят организовать импортозамещение, но и окажут информационное давление на иностранных производителей для сохранения импорта.

Ключевые слова: *медицинский суверенитет; малоинвазивная гастростомия; импортозамещение; отечественные разработки.*

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INTRODUCTUON

State sovereignty requires the state to be able to autonomously meet its inhabitants' basic necessities. The health-care system plays a key role in this process. In addition to ensuring that the population is demographically balanced, its goal is to give all citizens access to healthcare. Including palliative care for terminally ill patients. Modern medical technology makes it possible to effectively provide medical care and minimize the impact on the patient. An example would be a gastrostomy puncture, in which the damage to the patient's tissues is confined to the area of the nascent nutritious fistula [1]. At the same time, traditional surgery via laparotomy [2–4] continues to be extensively used, which is more traumatic than gastrostomy itself. This phenomenon can be caused by the low availability of the necessary imported consumables, not just by the individual anatomical characteristics of patients. The price, which is initially expressed in foreign currency, increases when the final value is created and transferred from the foreign manufacturer to the domestic consumer. That is why, in the Russian Federation, puncture gastrostomy is used less often than in countries where the production of necessary consumables is localized. At the same time, the possibility of sanctions restricting imports remains. That has negatively affected the availability of modern puncture methods for gastrostomies. Therefore, in order to expand the number of minimally invasive gastrostomies available, a preventive set of steps is required.

THE PURPOSE OF THE ARTICLE

The article is aimed to propose ways to achieve medical sovereignty on the example of minimally invasive gastrostomy.

MATERIALS AND METHODS

The article describes the results of the thesis research work carried out at the Department of General Medical Practice of the Saint Petersburg State Pediatric Medical University (SPSPMU). The study was carried out with all the necessary conditions and was approved by the Ethics Committee of the University.

The formation of hypotheses was carried out by processing the data from the literature and the results of experiments with the help of well-known methods of cognition: analysis, synthesis, abstraction, generalization, induction, deduction, etc.

Prototypes of the inventions were made of biologically inert materials: stainless steel and silicone, authorized for use in the food industry.

To confirm the hypotheses and experimental testing of developments, we used simulation of the processes studied in simulation conditions *in vitro*. Conducted experiments on laboratory animals in the conditions of the experimental operating department of operative surgery and topographic anatomy named after Prof. F.I. Valker.

The clinical part of the work was carried out at the city hospital №26, where the SPSPMU base is located.

RESULTS

A special gastrostomy tube has been given as a key part of studying imported specialized sets for percutaneous puncture gastrostomy under the control of endoscopy by the pull method. The remaining elements of the kits can be replaced by standard reusable tools and consumables available in a conventional surgical facility. In the course of scientific research, the gastronomic tube is divided into three components, and their original analogues have been developed: a device for inserting a gastronomic tube through the front wall of the abdomen (patent RU 2669483 C1); a device for fixing the tube externally in the fistula of the stomach and small intestine for feeding and decompression, stopping the tube from moving into the hollow organ through the fistula (patent RU 2759574 C1); a device for forming the internal

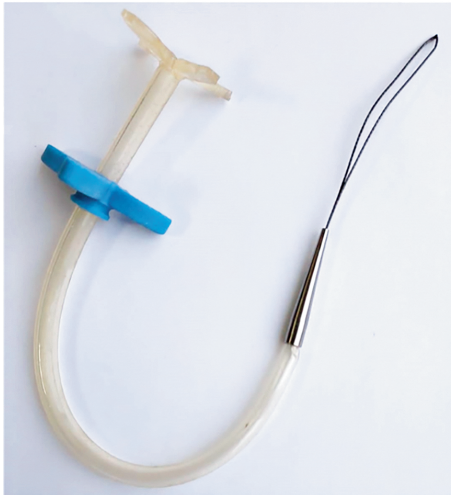

Fig. 1. Prototype of the original gastrostomy tube for percutaneous endoscopic gastrostomy, consisting of the developed products

Рис. 1. Прототип оригинальной гастростомической трубки для чрескожной эндоскопической гастростомы, состоящий из разработанных изделий

framework of the artificial fistula of the stomach and small intestine for nutrition and decompression (patent RU 2730978 C1) (Fig. 1).

The inventions' prototypes have been tested successfully on a simulator made for puncturing the stomach and the front wall of the abdomen during percutaneous endoscopic gastrostomy (patent RU 2765110 C1) [5] and on rabbits (Fig. 2, 3) [6].

Theoretical and experimental data obtained during the research allowed us to develop an alternative method of minimally invasive gastrostomy: minimal gastrostomy through mini-laparotomy (patent RU 2745655 C1) [7]. In the operation, a pressure method for forming a gastropex fistula is used, similar to a puncture gastrostomy. The main difference is the use of another type of access: mini-laparotomy, which allows you to reduce intraoperative injury and perform the intervention without additional visualization tools.

Minimal gastrostomy through mini-laparotomy is distinguished by a simple intervention technique. A mini-laparotomy is performed in a projection of an average of 1/3 of the stomach body with an additional orientation on the arrangement of the gastric gas bubble on the X-ray of the abdominal organs. In patients with a thin layer of subcutaneous fat, a 3 cm-long incision is sufficient. After opening the abdomen, the edges of the wound are removed by Farabef's hooks, and the front stomach wall is pulled up to the abdominal wall or even removed from the wound. At 1.5 cm from the edges of the future opening in the stomach wall, stitches are applied, of which two suture arms are oriented along the axis of the wound of the anterior abdominal wall (Fig. 4).

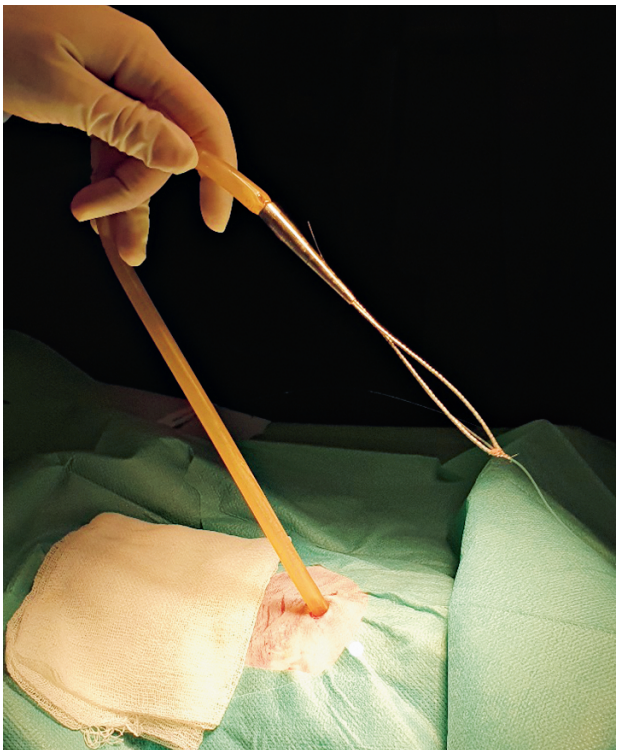

Fig. 2. Approbation of a device for conducting a gastrostomy tube through the anterior abdominal wall in an experimental percutaneous endoscopic gastrostomy in a rabbit

Рис. 2. Апробация приспособления для проведения гастростомической трубки через переднюю брюшную стенку в экспериментальной чрескожной эндоскопической гастростоме у кролика

Fig. 3. Approbation of the original external pressure plate during experimental percutaneous endoscopic gastrostomy in a rabbit

Рис. 3. Апробация оригинальной наружной прижимной пластинки при экспериментальной чрескожной эндоскопической гастростоме у кролика

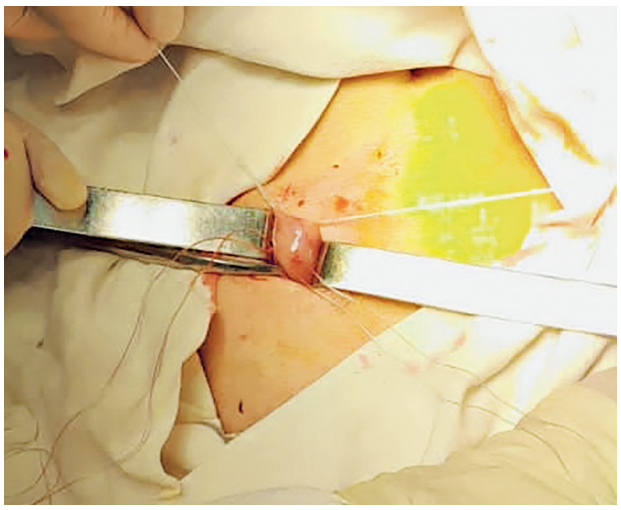

Fig. 4. Minimal gastrostomy through minilaparotomy: the stomach wall removed into the wound with 4 sutures-holders

Рис. 4. Минимальная гастростомия через мини-лапаротомию: выведенная в рану стенка желудка с 4 швами-держалками

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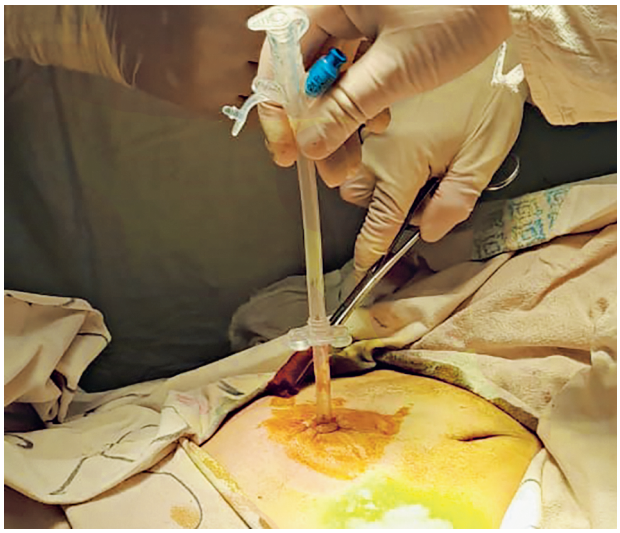

Fig. 5. Minimal gastrostomy via minilaparotomy: the final stage

Рис. 5. Минимальная гастростомия через мини-лапаротомию: завершающий этап

Between the suture holds, the stomach cavity is opened, and a gastrostonomic tube of the balloon type is started. The tube cylinder is filled in the opening of the stomach with water. The stomach wall is tightened behind the fixed tube to the abdominal wall, and the free ends of the suture are attached to the parietal peritoneum. The upper and lower joints along the wound are attached to the edges of the vaginal wall of the rectus. The surgical wound is then sutured, and the nutritional tube is fixed with an external pressure plate or by presentation to the skin (Fig. 5).

At the time of writing, the developed operation was successfully performed in 24 palliative patients with degree III–IV dysphagia, with no major complications requiring surgery.

DISCUSSION

The medical benefits of puncture gastrostomy due to its low invasiveness and the interest of disposable consumables manufacturers in expanding the market led to the rapid recognition and dissemination of the technique. At the same time, the economic efficiency of puncture gastrostomy decreases with distance from countries where the production of consumables is located. Compulsory import restrictions as a result of the sanctions policy formally reduce the market but preserve the income of foreign producers through parallel import technologies, so the economic damage is to the country against which the restrictions are imposed. At the same time, foreign producers are not interested in the emergence of competitive products on the market, so information on the readiness to organize Russian production stimulates the preservation of imports. At the time of writing, direct deliveries of specialized medical products for gastronomy from unfriendly countries remain.

In view of economic laws, the launch of domestic production against the background of the continued import of necessary medical products is not profitable in the short term. The use of alternative minimally invasive technology for the formation of nutritious fistulas is more advantageous both from an economic point of view and from the point of view of a value-oriented concept of health care.

Creating domestic versions of needed products and new ways to do the intervention can help lower reliance on imports. These ideas can be applied to other surgical technologies as well.

CONCLUSIONS

The developed original consumables for minimally invasive gasrostomy will not only allow for domestic production but will also put information pressure on foreign manufacturers to keep imports.

Minimal gastrostomy through mini-laparotomy does not require expensive imported consumables and can be considered a choice operation when puncture techniques are not available.

ADDITIONAL INFORMATION

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

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientifi c purposes).

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REFERENCES

1. Gavshchuk M.V., Orel V.I., Lisovskii O.V. et al. Comparison of different gastrostomy methods according to objective criteria. University Therapeutic Journal. 2023; 5(1): 110–3.
2. Gavshchuk M.V., Gostimskij A.V., Zav'yalova A.N. i dr. Evolyutsiya gastrostomy v palliativnoy meditsine. [The evolution of gastrostomy in palliative medicine]. Vestnik Rossijskoj voenno-medicinskoj akademii. 2018; 4(64): 232–6. (In Russian).
3. Gavshchuk M.V., Lisovskii O.V., Gostimskii A.V. i dr. Khirurgicheskiye metody korrektsii disfagii u vzroslykh palliativnykh bol'nykh po dannym sistemy OMS. [Surgical methods of dysphagia correction in adult palliative patients according to the data of the compulsory health insurance system]. Meditsina i organizatsiya zdravookhraneniya. 2021; 6(2): 21–6. (In Russian).
4. Zavyalova A.N., Gavshchuk M.V., Novikova V.P. i dr. Analiz sluchayev gastrostomii u detey po dannym sistemy obyazatel'nogo meditsinskogo strakhovaniya v Sankt-Peterburge. [Analysis of cases of gastrostomia in children according to the data of the system of compulsory health insurance in Saint Petersburg]. Voprosy dietologii. 2021; 11(4): 15–22. DOI: 10.20953/2224-5448-2021-4-15-22. (In Russian).
5. Gavshchuk M.V., Gostimskii A.V., Lisovskii O.V. i dr. Simulyatsionnaya uchebnaya metodika vypolneniya chreskozhnoy endoskopicheskoy gastrostomii. [Simulation training technique for performing percutaneous endoscopic gastrostomy]. Vestnik hirurgii im. I.I. Grekova. 2020; 179(6): 50–4. DOI: 10.24884/0042-4625-2020-179-6-50-54. (In Russian).
6. Gavschuk M.V., Gostimskii A.V., Bagaturiya G.O. i dr. Vozmozhnosti importozameshcheniya v palliativnoy meditsine. [Import Substitution Possibilities in Palliative Medicine]. Pediatrician. St. Petersburg. 2018; 9(1): 72–6. DOI: 10.17816/PED9172-76. (In Russian).
7. Gavshchuk M.V., Lisovskii O.V., Gostimskii A.V. i dr. Klinicheskiye nablyudeniya minimal'noy gastrostomii cherez minilaparotomiyu u palliativnykh bol'nykh. [Clinical observations of minimal gastrostomy through minilaparotomy in palliative patients]. Acta Biomedica Scientifica. 2022; 7(1): 182–8. DOI: 10.29413/ABS.2022-7.1.21. (In Russian).

ЛИТЕРАТУРА

1. Gavshchuk M.V., Orel V.I., Lisovskii O.V. et al. Comparison of different gastrostomy methods according to objective criteria. University Therapeutic Journal. 2023; 5(1): 110–3.
2. Гавщук М. В., Гостимский А. В., Завьялова А.Н. и др. Эволюция гастростомы в паллиативной медицине. Вестник Российской военно-медицинской академии. 2018; 4(64): 232–6.
3. Гавщук М.В., Лисовский О.В., Гостимский А.В. и др. Хирургические методы коррекции дисфагии у взрослых паллиативных больных по данным системы ОМС. Медицина и организация здравоохранения. 2021; 6(2): 21–6.
4. Завьялова А.Н., Гавщук М.В., Новикова В.П. и др. Анализ случаев гастростомии у детей по данным системы обязательного медицинского страхования в Санкт-Петербурге. Вопросы диетологии. 2021; 11(4): 15–22. DOI: 10.20953/2224-5448-2021-4-15-22.
5. Гавщук М.В., Гостимский А.В., Лисовский О.В. и др. Симуляционная учебная методика выполнения чрескожной эндоскопической гастростомии. Вестник хирургии им. И.И. Грекова. 2020; 179(6): 50–4. DOI: 10.24884/0042-4625-2020-179-6-50-54.
6. Гавщук М.В., Гостимский А.В., Багатурия Г.О. и др. Возможности импортозамещения в паллиативной медицине. Педиатр. 2018; 9(1): 72–6. DOI: 10.17816/PED9172-76.
7. Гавщук М.В., Лисовский О.В., Гостимский А.В. и др. Клинические наблюдения минимальной гастростомии через минилапаротомию у паллиативных больных. Acta biomedica scientifica. 2022; 7(1): 182–8. DOI: 10.29413/ABS.2022-7.1.21.

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CLINICAL CASE OF LOWER RESPIRATORY TRACT INFECTION CAUSED BY *ELIZABETHKINGIA MENINGOSEPTICA* IN A CHILD WITH CEREBRAL PALSY

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Abstract. The most common cause of morbidity and mortality in patients with cerebral palsy (CP), both in children and adults, is associated with respiratory diseases. Patients with CP are characterized by a decrease in local immunity of the upper and lower respiratory tract, increased viral diseases, a progression of bacterial infection without additional infection or increase in the count of microbial numbers, decrease in lung function, and infection of the respiratory tract with a microbiota, which is atypical for practically healthy children. CP is a disease that occurs with severe comorbid conditions as epilepsy, requiring constant basic therapy, accompanied by standard negative side effects. Both severe gastrointestinal disorders and associated severe disorders of nutritional status, deficient conditions contribute to infectious process against the background of CP. A clinical observation of the patient with CP who had severe community-acquired pneumonia caused by *Elizabethkingia meningoseptica*, which developed while taking glucocorticosteroids, was described. The difficulties of managing of the child who was prescribed empirical antimicrobial therapy, and successful eradication of the pathogen with clinical and radiological recovery after a detection of *Elizabethkingia meningoseptica* in the bronchoalveolar lavage fluid and using the appointment antibiotic therapy based on the results of the obtained antibiogram were described. The authors paid attention to the pathogenetic features of the implementation of respiratory and nutritional disorders in a cohort of patients with CP and the need to personalize diagnostic and therapeutic measures in each case.

Key words: *pneumonia; cerebral palsy; children; Elizabethkingia meningoseptica; nutritional status; antibiotic resistance.*

КЛИНИЧЕСКИЙ СЛУЧАЙ ИНФЕКЦИИ НИЖНИХ ДЫХАТЕЛЬНЫХ ПУТЕЙ, ВЫЗВАННОЙ *ELIZABETHKINGIA MENINGOSEPTICA*, У РЕБЕНКА С ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ

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Резюме. Наиболее частая причина заболеваемости и смертности больных детским церебральным параличом (ДЦП), в том числе в детском возрасте, связана с заболеваниями органов дыхания. Для больных ДЦП характерно снижение местного иммунитета верхних и нижних дыхательных путей, повышение вирусной заболеваемости, прогрессирование бактериальной инфекции без дополнительного инфицирования или увеличения количества микробов, снижение функции легких, инфицирование дыхательных путей с микрофлорой, нетипичной для практически здоровых детей. ДЦП — заболевание, протекающее с тяжелыми коморбидными состояниями: это эпилепсия, требующая постоянной базисной терапии, сопровождающаяся стандартными негативными побочными эффектами, это как тяжелые желудочно-кишечные расстройства и связанные с ними тяжелые нарушения нутритивного статуса, так и дефицитные состояния, способствующие инфекционному процессу на фоне ДЦП. Описано клиническое наблюдение больного ДЦП, перенесшего тяжелую внебольничную пневмонию, вызванную *Elizabethkingia meningoseptica*, развившуюся на фоне приема глюкокортикостероидов. Описаны трудности ведения ребенка при назначении эмпирической антимикробной терапии и успешная эрадикация возбудителя при клинико-рентгенологическом выздоровлении больного после обнаружения *Elizabethkingia meningoseptica* в жидкости бронхоальвеолярного лаважа и назначения антибиотикотерапии по результатам полученной антибиотикограммы. Авторы обращают внимание на патогенетические особенности реализации нарушений дыхания и питания в когорте больных ДЦП и необходимость персонализации диагностических и лечебных мероприятий в каждом случае.

Ключевые слова: *пневмония; детский церебральный паралич; дети; Elizabethkingia meningoseptica; нутритивный статус; антибиотикорезистентность.*

INTRODUCTION

The most common cause of morbidity and mortality in patients with cerebral palsy (CP), both in children and adults, is associated with respiratory diseases [1]. Compared to the general population, adults and children with CP have a 14-fold increased risk of fatal outcome from respiratory diseases [2]. Nowadays, both the duration and quality of life in children with CP are increasing because of the improvement of treatment and rehabilitation technologies. Therefore, long-term follow-up of patients, correction of chronic respiratory disorders and related nutritional status disorders, which largely determine the lung function, become more important [1]. Infectious diseases in children with CP due to impaired immunity, severe gastroesophageal motility disorders, decreased functional activity of mucosal immunity, mucociliary clearance disorders, are atypical, often subclinical. The respiratory failure has been being the main cause of death in this population since the 1970's [3]. In addition, CP is often accompanied by tracheobronchomalacia and other upper and lower airway abnormalities, exacerbating mucociliary transport dysfunction, which increases the need for bronchodilators, antibiotics, anti-inflammatory and mucolytic therapy. Patients with CP are characterized by decreased local immunity of the all respiratory tract, an increased level of viral diseases, progression of bacterial infections without additional infection or increased microbial counts, decreased lung function (FEV1 and VC) and age (catamnesis from 8 to 18 years), and infection of the respiratory tract with atypical microbiota for practically healthy children [4–8]. The course of respiratory tract infection in this category of children has some pathogenetic and clinical features, as well as the associated difficulties of diagnosis and therapy, which are illustrated by the present clinical case.

CLINICAL CASE

The patient K., aged 1 year and 1 month, was under medical observation.

Clinical diagnosis

Main disease. Severe, uncomplicated community-acquired right-sided pneumonia of the upper and middle lobes, Elizabethkingia meningoseptica-etiology, prolonged course.

Concomitant diseases. Epilepsy caused by mutation of the *GNAO1* gene. Cerebral palsy, spastic diplegia. Gross Motor Functional Classification (GMFCS) Level V, Manual Ability Classification System (MACS) Level V, Communication Function Classification System (CFCS) Level V, Drinking Ability Classification System (EDACS) Level V. Dystonic attacks. Bulbar syndrome. Microcephaly. Severe malnutrition. Severe malabsorption. Anemia of chronic diseases, II degree.

Anamnesis morbi The child fell ill acutely, the disease began with a fever up to 38.5 °C, reduced with paracetamol, the maximum temperature was up to 40.0 °C, against this background there was a refusal to eat and drink, parents called an ambulance. The child was taken by the ambulance doctors and hospitalized in the pediatric department of the children's multidisciplinary hospital at the place of his residence.

Anamnesis vitae. The mother is 26 years old, the father is 29 years old, both of them are healthy. A boy is from the second pregnancy. The eldest sib (first pregnancy), aged 2 years, is practically healthy. The present pregnancy occurred with a retrochorial hematoma in the first trimester. Births at term was by caesarean section due to pelvic position. The birth weight was 3470 g and the length was 54 cm. From the second day of life the child has neonatal jaundice and received phototherapy in the maternity hospital. The duration of stay in the maternity hospital was 5 days. The jaundice was ended on its own after three weeks. A breastfeeding was until one month of age. From the 5th day of life, seizures appeared and manifested as shudders and clutching. From 1.5 months of age there were convulsions with spasms and tonic-clonic component, which became more frequent with each month. At the age of 2 months, the child was examined in the psychoneurological department; according to the results of magnetic resonance imaging (MRI) of the brain, congental biventriculomegaly was diagnosed; according to the results of electroencephalography (EEG), diffuse changes in brain activity, diffuse epileptic activity in the background and with elements of suppression were revealed. The diagnosis of epilepsy was verified; molecular genetic examination revealed an amino acid substitution in exome 7 of a GNAO1 gene in a heterozygous variant. During the first and second six months of life, convulsive seizures became more frequent, and anticonvulsant therapy was corrected: doses of valproate acid were increased, and levetiracetam was used. The frequency of epileptic seizures, despite therapy, continued to increase, so a month before the development of the present acute illness, an epileptologist performed pulse therapy with glucocorticosteroids (GCS). At the time of the hospitalization the child received prednisolone (1 mg/kg/day) as a reduction of GCS dosage. In addition to the neurological clinical picture, the child had significant problems with food intake. Against the background of the course of epilepsy and progressive brain damage, pronounced motor disorders and severe difficulties in eating were formed. It corresponded to GMFCS V, MACS V, CFCS V, EDACS V. Pronounced dystonic attacks and pain syndrome persisted. The presence of marked bulbar syndrome was accompanied by persistent lower respiratory tract infections, which were treated on an outpatient basis; antibacterial drugs was used *per os* every month (aminopenicillins with beta-lactamase inhibitor, cephalosporins (CS) II and III generations, macrolides). The parents refused to gastrostomy feeding, which increased malnutrition, and by the age of 1-year patient K. had severe protein-energy malnutrition (PEM). In addition, the intake of food and fluids by mouth constantly provoked and maintained the course of catarrhal-purulent endobronchitis. The patient had been a child with disability since 4 months of age and had palliative status since 8 months of age.

The patient's condition on admission is severe due to neurologic clinical picture, respiratory disorders (saturation 93–94%, tachypnea 70–74 per minute, participation of auxiliary breathing muscles, increased amounts of sputum and frequent cough), intoxication (refusal to eat and drink, fever 39.6 °C, skin pallor), severe malnutrition (an absence of subcutaneous fat, a decreased skin turgor, a weight — 6400 g, a height — 74 cm, the deficiency of weight — 36%). The state of health suffers due to the disease. During the examination there are no seizures, there are some dystonic attacks as a short-term hypertonicity of trunk muscles, limbs, head shaking, at rest a moderately increased tone in extensors of limbs, clonus of feet. Palpebral fissures are equal, pupils S=D, of medium size, no nystagmus, the gaze does not fixate and follow. Nasolabial folds are symmetrical. A feeding was through a baby bottle. A child was sucking slowly and regurgitated 50–60 ml of formula, the choking was frequent. Signs of severe physical and psychomotor delay: the child does not hold his head and sit up. A patient does not react to the surrounding environment. Meningeal signs are negative; the child have severe drowsiness. When

the patient stays awake he has slow reactions as opening of eyes, movements of limbs or short-term dystonic attacks while examination. The skin was pale, dry, there was no rash, but there was an acrocyanosis. A subcutaneous fat layer was practically absent on the limbs, anterior abdominal wall and face. Nasal breathing was difficult, there was a lot of mucous discharge from the nasal passages. There was a moderate hyperemia of the posterior pharyngeal wall, its loosening and there were not plaques. Peripheral lymph nodes were up to 5–7 mm without changes in other properties. The tongue root was moist and covered with white plaque. Mucous membranes of the oral cavity were pink, moist and clean. The voice was sonorous. The cough was frequent with variable productivity. The percussion sound over the lungs was with a bandbox sound, on the right side was total dulled. While auscultation the breathing was bronchial, multicaliberal crackle sounds were on the left, diminished breath sounds were on the right. Heart tones were loud, rhythmic. The abdomen was somewhat sunken, soft and painless. The liver was +1,5+1,5-1/3, its edge was painless, elastic. Spleen was not enlarged. The defecation did not occur independently, it appeared only after microlax. The fecal was yellow, mushy and without pathologic impurities. There were no urination problems, it was free, there was no edema. It should be noted that in addition to oxygen therapy via binasal cannulae, antiviral, antibacterial therapy (ABT) with 3rd generation of CS and continuation of prednisolone *per os* in the previous dose (1 mg/kg/day), infusion therapy with 30 mg of prednisolone was prescribed by the doctor on duty. The patient had been receiving this infusion therapy for 7 days from the moment of hospitalization. It was done for the "detoxification" as indicated in the medical documents. A complete clinical and laboratory examination of the patient was performed; the diagnosis of pneumonia was confirmed by the X-rays result (Fig. 1). On the first day of hospitalization, which coincided with the first day of illnesses, inflammatory infiltration in the projection of the upper and middle lobes of the right lung was detected.

After starting ABT with 3rd generation of CS there was no positive clinical dynamics. Therefore, the first change of ABT (combination of ampicillin/sulbactam, aminoglycoside and macrolide) was performed because of the severe course of pneumonia (Table 1). The results of bacteriologic cultures of sputum and blood were negative. On the 10th day of hospitalization the highest mark-

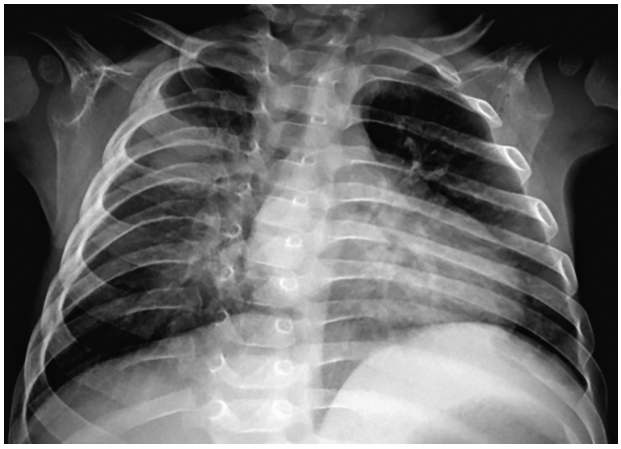

Fig. 1. X-ray picture on day first of hospitalization
Рис. 1. Рентгенологическая картина в первые сутки госпитализации

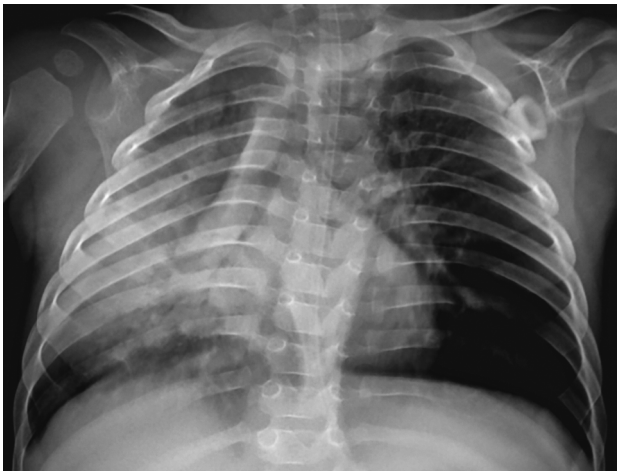

Fig. 2. X-ray picture on the 10th day of hospitalization
Рис. 2. Рентгенологическая картина на 10-е сутки госпитализации

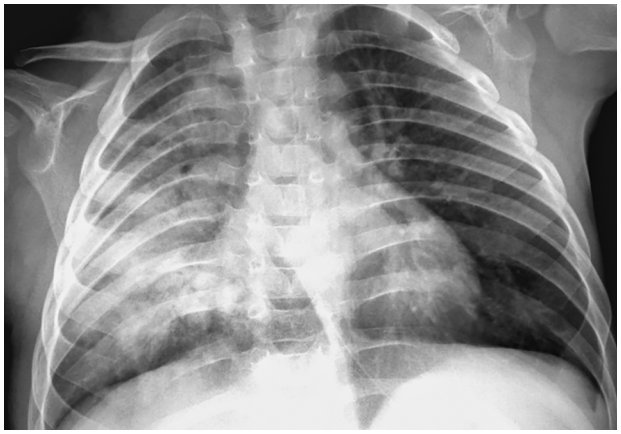

Fig. 3. X-ray picture on the 30th day of hospitalization
Рис. 3. Рентгенологическая картина на 30-е сутки госпитализации

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Table 1. Dynamics of clinical and laboratory parameters and antimicrobial therapy during hospitalization

Таблица 1. Динамика клинико-лабораторных показателей и антимикробной терапии в период госпитализации

Parameters	Day of hospitalization										
	1 day	5 day	10 day	15 day	20 day	25 day	30 day	35 day	40 day	45 day	50 day
Dynamics of clinical picture											
Temperature, °C	40,2	39,5	39,3	38,7	38,9	38,5	38,7	37,7	36,5	36,6	36,6
Cough	+++	+++	+++	+++	+++	+++	+++	++	+	+	+
Sputum	+++	+++	+++	+++	+++	+++	+++	++	+	+	+
Refusal to eat or drink	+++	+++	+++	+++	+++	+++	+++	++	–	–	–
Dynamics of laboratory markers											
White blood cells, 10^9/L	18,9	25,6	30,4	27,7	24,3	25,5	29,6	15,6	8,9	7,5	7,3
Neutrophil index	0,24	0,23	0,27	0,25	0,22	0,23	0,24	0,18	0,15	0,14	0,10
CRP, mg/l	78,4	86,4	93,8	77,5	68,9	81,5	88,9	21,2	4,0	3,0	4,0
PCT, ng/l		8,0	12,0	8,0	11,0			2,0	>0,2		
Dynamics of microbiological monitoring											
No colony growth	+	+	+	+		+	+		+	+	+
Staphylococcus aureus, sputum, CFU/mL					10^5						
Elizabethkingia meningoseptica, BAL, CFU/mL								10^7			
Antimicrobial and other treatment											
Cefotaxime	+										
Ampisid +amicacine + sumamed		+									
Meropenem+vancomycin			+								
Immunoglobulins intravenous			+								
Amoxiclav+cephoperazone/sulbactam				+							
Zinforo+fluconazole					+						
Ceftazidime+metronidazol+vifend +vil prafen						+	+				
Ciprofloxacin+ piperacillin/tazobactam+biseptol								+	+	+	+

ers of systemic inflammation, including total leukocytosis, neutrophil index, the highest level of C-reactive protein (CRP) and procalcitonin (PCT) were registered, clinical and radiological dynamics was also negative (Table 1, Fig. 2).

Then, during the hospitalization, a patient K's condition remained stably severe due to respiratory disorders against the background of severe neurological clinical picture with frequent epileptic seizures and dystonic attacks, as well as severe malnutrition. All of that persisted and had no positive dynamics. Furthermore, during the first month of hospitalization the child's inflammatory activity was pronounced without a tendency to decrease, the result of bacteriological cultures was negative. And only on the 20th day of hospitalization the growth of Staphylococcus aureus 10^5 CFU/ml with preserved sensitivity to benzylpenicillin and cefoxitin was detected in the sputum. Anti-staphylococcal antibacterial drugs were already in the ABT, ceftaroline fosamil was given to the child, but there was no positive clinical and X-ray effect (Fig. 3).

Table 2. Antibioticogram of *Elizabethkingia meningoseptica,* 10^7 CFU/ml, obtained as a result of bacteriological culture of broncho-alveolar lavage fluid

Таблица 2. Антибиотикограмма *Elizabethkingia meningoseptica,* 10^7 КОЕ/мл, полученная в результате бактериологического посева бронхоальвеолярной лаважной жидкости

Antimicrobial drug	Minimum inhibitory concentration, mgc/mL	Interpretation
Aztreonam	>32	R
Amikacin	>32	R
Ampicillin/sulbactam	>16/8	R
Ampicillin	>16	R
Gentamicin	>8	R
Imipenem	>8	R
Levofloxacin	<=2	S
Meropenem	>8	R
Nitrofurantoin	>64	R
Piperacillin	>64	R
Piperacillin/Tazobactam	<=16	S
Tobramycin	>8	R
Cefepime	>16	R
Cefotaxime	>32	R
Cefotaxime/clavulanate	4	S
Cefotetan	>32	R
Cefoperazone/ sulbactam	2	S
Ceftazidime	>16	R
Ceftriaxone	>32	R
Cefuroxime	>16	R
Cephalothin	>16	R
Ciprofloxacin	<=1	S
Ertapenem	>4	R
Tetracycline	8	I
Trimethoprim/ sulfometaxazole	<=2/38	S

After 4 weeks of unsuccessful ABT of community-acquired pneumonia, patient K. underwent therapeutic and diagnostic bronchoscopy with collection of bronchoalveolar lavage fluid (BAL) and it sowing on standard nutrient media to detect fungi and Mycobacterium tuberculosis. On the 35th day of the hospitalization, a conclusion was made about the presence of abundant growth of Elizabethkingia meningoseptica (107 CFU/ml) with the results of sensitivity to ABT shown in Table 2. Then, ABT was prescribed according to the obtained antibioticogram (Table 1). After use of combined therapy with ciprofloxacin and piperacillin/tazobactam with trimethoprim/sulfometaxazole for two weeks, a positive dynamics of clinical picture was achieved. It became noticeable on the 2–3 rd day, and complete radiological resolution of the process was achieved on the 50th day of hospitalization (Fig. 4).

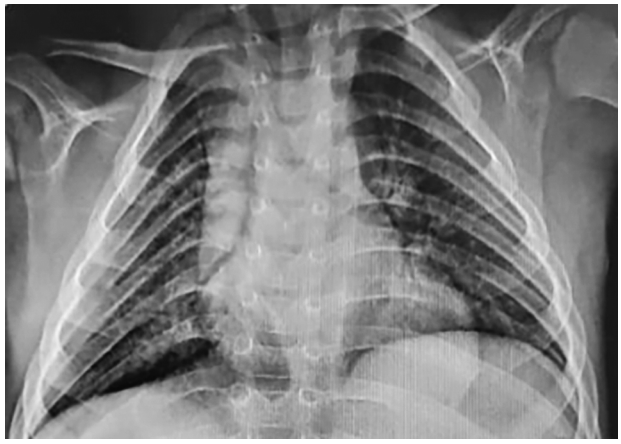

Fig. 4. X-ray picture on the 50th day of hospitalization
Рис. 4. Рентгенологическая картина на 50-е сутки госпитализации

The patient K. was discharged to the outpatient stage on the 58th day with clinical and radiological recovery. Recommendations for treatment of the underlying diseases, including gastrostomy placement, were provided. The result of Mycobacterium tuberculosis (MBT) culture was negative. Currently, the child is a gastrostomy carrier. He undergoes palliative care and rehabilitation every 6 months. There were no episodes of lower respiratory tract infections for the last year. K. receives ABT courses for intercurrent infections no more than 1–2 times a year. Further medical observation of the patient continues.

DISCUSSION

The presence of severe motor disorders on the background of cerebral palsy regardless of its cause determines the formation of chronic lung diseases, atypical and subclinical course of acute infectious bronchopulmonary inflammation due to different factors (Fig. 5, 6). Muscle control impairment, dystonic attacks increase dysphagia and microaspiration [6–8].

In turn, gastrointestinal dysfunction appears due to motor and neurological problems and is

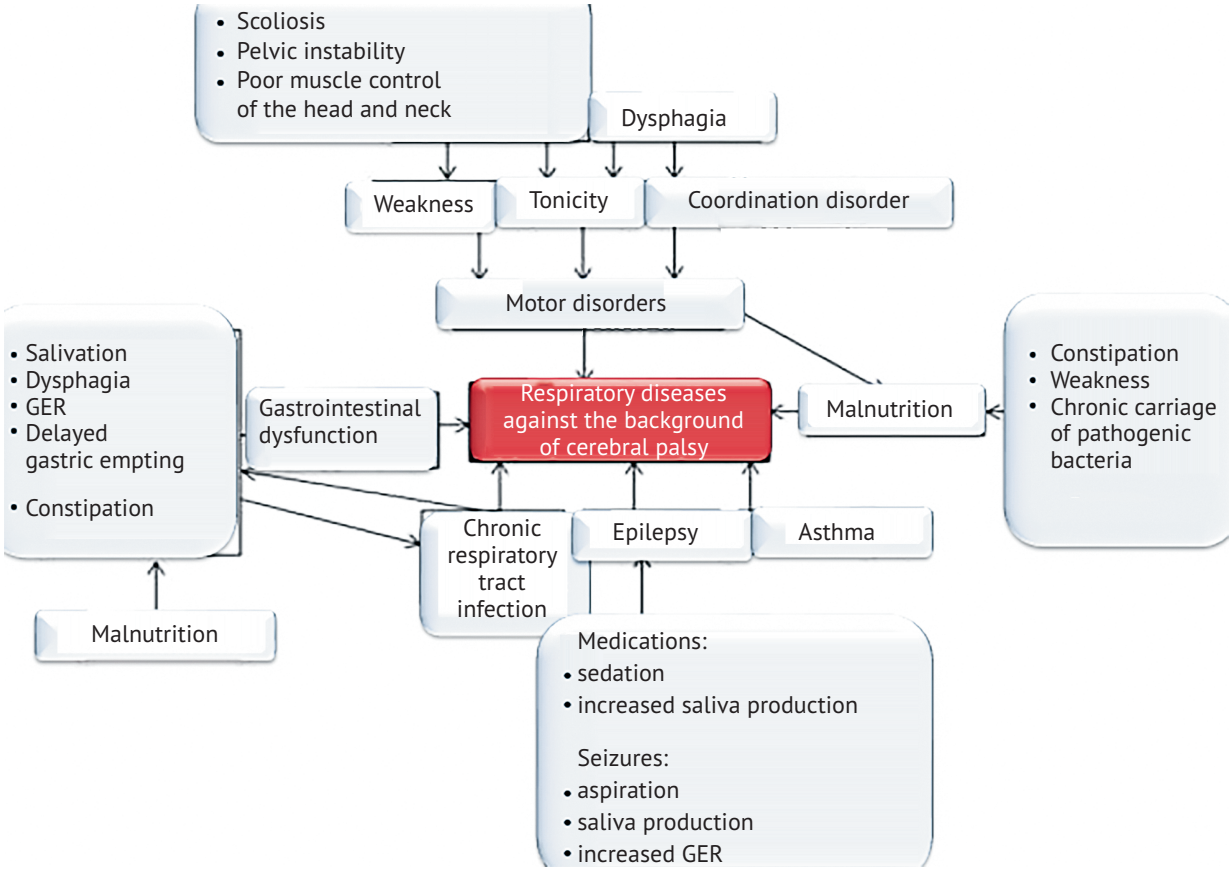

Fig. 5. Pathogenesis of the development and progression of respiratory disorders against the background of cerebral palsy
Рис. 5. Патогенез развития и прогрессирования респираторных нарушений на фоне церебрального паралича

common in both upper gastrointestinal (GI) tract (it manifests by hypersalivation, choking, aspiration, gastric hypomotility, gastroesophageal reflux) and lower GI tract. There it is shown as chronic constipation, bacterial overgrowth syndrome, malnutrition and malabsorption [6–8]. Moreover, taking medications, including anticonvulsants and cholinergic blocking drug, has certain classical side effects that increase a count of functional GI disorders [6–8].

All patients suffering from CP with class V in motor disorders have malnutrition, associated severe nutritional status disorders and severe malabsorption (Fig. 6). All this conditions are expressed not only in delayed physical development, growth and body weight delay, but also in the formation of numerous deficiency states including disorders of calcium-phosphorus homeostasis with changes in bone mineral density. In turn, a patient has a severe chronic pain syndrome, which presented in children due to dystonic attacks. Disorders of iron metabolism affect the immune system, and the developing hypoxia due to an iron deficiency aggravates respiratory failure, associated with bronchopulmonary diseases [6–8]. The patient we observed had severe protein-energy malnutrition and anemia, as well as osteoporosis, which is well visualized by X-ray.

Patient K. had severe motor disorders on the background of CP, and therefore, he had all pathogenetic and clinical factors affecting the onset and progression of respiratory and nutritional disorders. Thus, it should be noted that chronic colonization of atypical microbiota and/or bacterial overgrowth syndrome should be considered as an independent risk factor for severe infectious process in this category of patients. The use of GCS repeatedly increases infectious complications, if a patient has severe diseases. The classic example is GCS therapy for severe bronchopulmonary dysplasia to reduce the dependence on respiratory support at the stage of neonatal intensive care units [9]. Patient K. received pulse therapy with GCS for refractory seizure syndrome before the pneumonia, and then continued to receive GCS in the standard dose. In addition, treatment with prednisolone was continued both orally and parenterally despite the detection of pneumonia after chest

radiography. This fact aggravated the existing immunosuppression, and probably played a role in the progression of bronchopulmonary inflammatory infiltration and worsening of the patient's condition. Respiratory disorders were increased.

Gram-negative non-fermenting bacteria are frequent causative agents of chronic respiratory tract infection in children with severe CP [5]. Gram-negative bacteria of the genus *Elizabethkingia* are actual causative agents of hospital-acquired infections and are usually associated with high mortality [10, 11]. Recent publications have reported several cases of severe infection caused by this bacterium. The most common variant of disease was neonatal meningitis with septicemia and bacteremia. In addition, cases of osteomyelitis [15], urinary tract infections [16, 17], endogenous endophthalmitis [18], endocarditis [19], epididymo-orchitis [20], lung abscess [21], necrotizing fasciitis [22], cystic fibrosis [23], hydrocephalus [24], and secondary infections with high mortality, especially in immunocompromised patients [25], have been described. *Elizabethkingia meningoseptica* infections have also been in patients with COVID-19 [26]. *E. meningoseptica* affects not only immunocompromised individuals but also immunocompetent people [27]. Historically, the first report of human infection with *E. meningoseptica* was about 19 cases of meningitis in infants in the United States [28].

Our report shows that *E. meningoseptica* is specific to immunocompromised patients.

Both whole genome sequence analysis and optical mapping, MALDI-TOF mass spectrometry, led to a composition revision of the genus *Elizabethkingia* with the isolation of 8 species, named *E. meningoseptica*, *E. miricola*, *E. anophelis*, *E. bruuniana*, *E. ursingii*, *E. occulta* [29], *E. argenteiflava* [30] and the newest *E. umeracha* [31]. It is necessary to know that the identification of *Elizabethkingia* using traditional microbiological methods is difficult [32]. It accounts for the low detectability of this pathogen.

In case of the patient K., *E. meningoseptica* was detected only in the BAL, despite abundant sputum discharge. It occurred only on the 35th day of hospitalization, what confirms the difficulty of

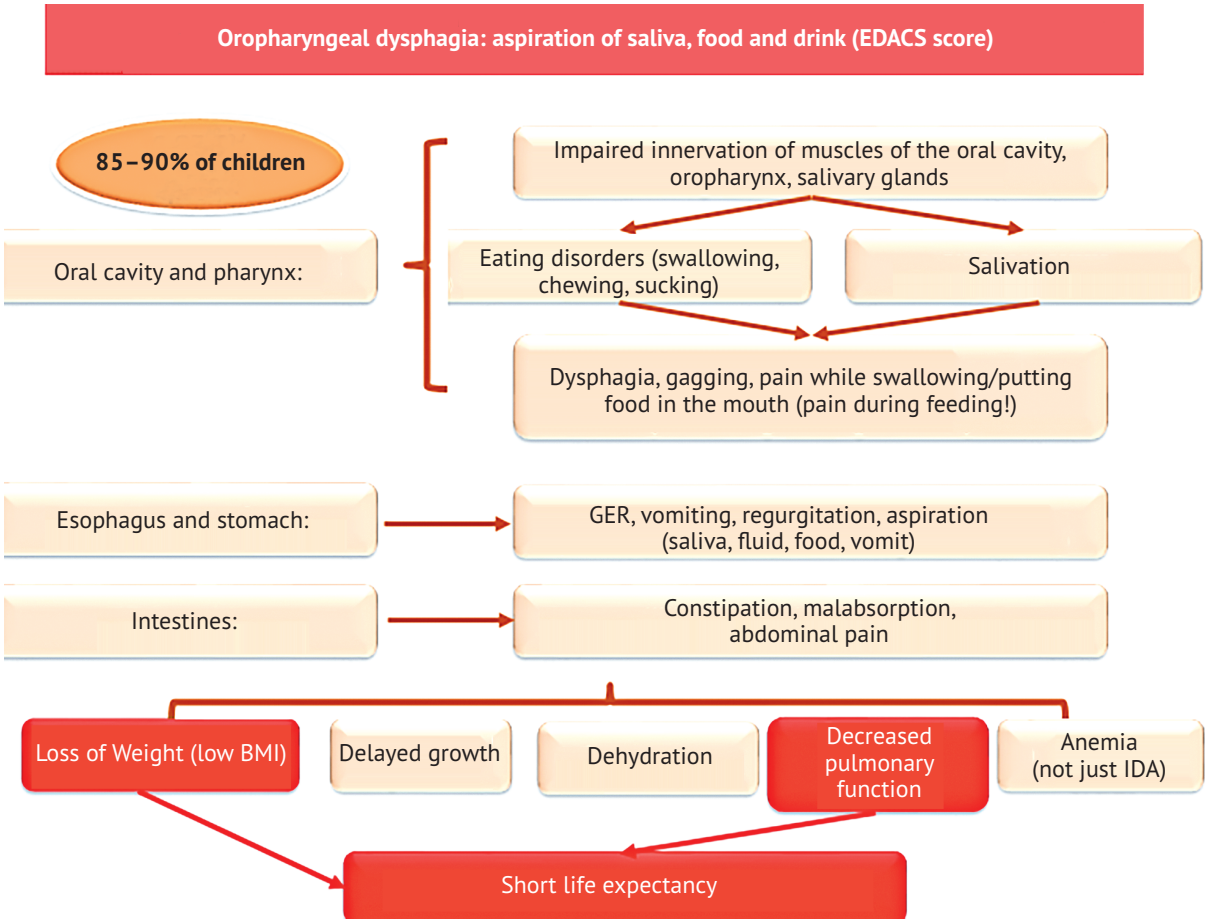

Fig. 6. Pathogenesis of the development and progression of nutritional disorders against the background of cerebral palsy
Рис. 6. Патогенез развития и прогрессирования нутритивных нарушений на фоне церебрального паралича

identification of this pathogen. This consists to already published data [32].

Members of the genus *Elizabethkingia* are resistant to most β-lactams, inhibitor-protected β-lactams and carbapenems because of the presence of two unique class B metallo-β-lactamases (MBL), namely blaBlaB and blaGOB, and also a class A extended-spectrum β-lactamase (ESBL) — blaCME [33].

According to given recommendations "Determination of susceptibility of microorganisms to antimicrobial agents" version 2021-01, *E. meningoseptica* has natural resistance to the antibacterial drugs: ampicillin, amoxicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, ticarcillin, ticarcillin/clavulanic acid, piperacillin, cefazolin, cephalothin, cephalexin, cefadroxil, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefepime, aztreonam, ertapenem, imipenem, meropenem, and polymyxin. *Elizabethkingia* spp. isolates are often resistant to aminoglycosides, macrolides, tetracycline, and vancomycin, but can remain sensitivity to piperacillin/tazobactam, fluoroquinolones, minocycline, tigecycline, trimethoprim/sulfamethoxazole [34, 35] and levofloxacin [36]. Nowadays, there are no established criteria for assessing antimicrobial sensitivity for members of the genus Elizabethkingia. In our study the results were interpreted in terms of borderline MIC values by the EUCAST 2022 criteria for Pseudomonas spp. and Enterobacteriaceae, due to the lack of defined borderline values for *E. meningoseptica*.

The isolate of E. meningoseptica was sensitive to fluoroquinolones, piperacillin/tazobactam, cefoperazone/sulbactam and trimethoprim/sulfamethoxazole, therefore a combination of three antibacterial drugs was prescribed taking into in view of the possible production of MBL and ESBL. The child was prescribed off-label ciprofloxacin, piperacillin/tazobactam and trimethoprim/sulfamethoxazole.

CONCLUSION

Thus, the clinical observation demonstrates a severe course of community-acquired pneumonia caused by the infrequently diagnosed pathogen *E. meningoseptica* in a patient with severe comorbid pathology in the form of cerebral palsy and its complications, as well as risk factors for generalization of the infectious process associated with the usage of glucocorticosteroids against the background of active bacterial infection. This clinical observation pays attention of practitioners to the peculiarities of microbial colonization of the respiratory tract in children with severe cerebral palsy. It shows a need for earlier usage of invasive diagnostic procedures (bronchoscopy) with targeted microbiological diagnosis of bronchoalveolar lavage fluid for identification of pathogens by microbiological routine methods.

ADDITIONAL INFORMATION

Author contribution. E.V. Loshkova — patient management and preparation of extracts from medical records, analysis of literature data and their interpretation, structuring of the material and writing of the article; A.V. Lyamin — interpretation of the results of microbiological studies and their discussion, verification and structuring of the article; G.N. Yankina — discussion of the article; T.S. Lyulka — technical support and discussion of the manuscript. All authors read and approved the final version before publication.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Е.В. Лошкова — ведение пациента и подготовка выписки из медицинской документации, анализ данных литературы и их интерпретация, структурирование материала и написание статьи; А.В. Лямин — интерпретация результатов микробиологических исследований и их обсуждение, проверка и структурирование статьи; Г.Н. Янкина — обсуждение статьи; Т.С. Люлька — техническое сопровождение и обсуждение рукописи. Все авторы прочли и одобрили финальную версию перед публикацией.

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REFERENCES / ЛИТЕРАТУРА

1. Rakocevic G., Alexopoulos H., Dalakas M.C. Quantitative clinical and autoimmune assessments in

stiff person syndrome: evidence for a progressive disorder. BMC Neurol. 2019; 19(1): 1.
2. Ryan J.M., Peterson M.D., Ryan N. et al. Mortality due to cardiovascular disease, respiratory disease, and cancer in adults with cerebral palsy. Dev Med Child Neurol. 2019; 61(8): 924–8.
3. Himmelmann K., Sundh V. Survival with cerebral palsy over five decades in western Sweden. Dev Med Child Neurol. 2015; 57(8): 762–7.
4. Myers L.L., Narminathan A., Fitzgerald D.A. et al. Transition to adult care for young people with cerebral palsy. Paediatr Respir Rev. 2020; 33: 16–23.
5. Gerdung C.A., Tsang A., Yasseen A.S. 3rd. et al. Association Between Chronic Aspiration and Chronic Airway Infection with Pseudomonas aeruginosa and Other Gram-Negative Bacteria in Children with Cerebral Palsy. Lung. 2016; 194(2): 307–14. DOI: 10.1007/s00408-016-9856-5. Epub 2016 Feb 16. PMID: 26883134.
6. Marpole R., Blackmore A.M., Gibson N. et al. Evaluation and Management of Respiratory Illness in Children With Cerebral Palsy. Front Pediatr. 2020; 8: 333. DOI: 10.3389/fped.2020.00333. PMID: 32671000; PMCID: PMC7326778.
7. Blackmore A.M., Bear N., Blair E. et al. Prevalence of symptoms associated with respiratory illness in children and young people with cerebral palsy. Dev Med Child Neurol. 2016; 58(7): 780–1.
8. Blackmore A.M., Bear N., Blair E. et al. Factors Associated with Respiratory Illness in Children and Young Adults with Cerebral Palsy. J Pediatr. 2016; 168: 151–7.e1.
9. Bonadies L., Zaramella P., Porzionato A. et al. Present and Future of Bronchopulmonary Dysplasia. J Clin Med. 2020; 9(5): 1539. DOI: 10.3390/jcm9051539. PMID: 32443685; PMCID: PMC7290764.
10. Govindaswamy A., Bajpai V., Trikha V. et al. Multidrug resistant Elizabethkingia meningoseptica bacteremia — Experience from a level 1 trauma centre in India. Intractable Rare Dis Res. 2018; 7(3): 172–6. DOI: 10.5582/irdr.2018.01077. PMID: 30181936; PMCID: PMC6119665.
11. Lau S.K., Chow W.-N., Foo C.-H. et al. Elizabethkingia anophelis bacteremia is associated with clinically significant infections and high mortality. Sci. Rep. 2016; 6: 26045. DOI: 10.1038/srep26045.
12. Dziuban E.J., Franks J.L., So M. et al. Elizabethkingia in children: A comprehensive review of symptomatic cases reported from 1944 to 2017. Clin. Infect. Dis. 2018; 67: 144–9. DOI: 10.1093/cid/cix1052.
13. Opota O., Diene S.M., Bertelli C. et al. Genome of the carbapenemase-producing clinical isolate Elizabethkingia miricola EM_CHUV and comparative genomics with Elizabethkingia meningoseptica and Elizabethkingia anophelis: Evidence for intrinsic multidrug resistance trait of emerging pathogens. Int. J. Antimicrob. Agents. 2017; 49: 93–7. DOI: 10.1016/j.ijantimicag.2016.09.031.
14. Swain B., Rout S., Otta S., Rakshit A. Elizabethkingia meningoseptica*:* An unusual cause for septicaemia. JMM Case Rep. 2015; 2: e000005. DOI: 10.1099/jmmcr.0.000005.
15. Lee C.-H., Lin W.-C., Chia J.-H. et al. Community-acquired osteomyelitis caused by Chryseobacterium meningosepticum: Case report and literature review. Diagn. Microbiol. Infect. Dis. 2008; 60: 89–93. DOI: 10.1016/j.diagmicrobio.2007.07.009.
16. Gupta P., Zaman K., Mohan B., Taneja N. Elizabethkingia miricola: A rare non-fermenter causing urinary tract infection. World J. Clin. Cases. 2017; 5: 187. DOI: 10.12998/wjcc.v5.i5.187.
17. Raghavan S., Thomas B., Shastry B. Elizabethkingia meningoseptica*:* Emerging multidrug resistance in a nosocomial pathogen. Case Rep. 2017; 2017: bcr-2017-221076. DOI: 10.1136/bcr-2017-221076.
18. Young S.M., Lingam G., Tambyah P.A. Elizabethkingia meningoseptica Engodenous Endophthalmitis — A Case Report. Antimicrob. Resist. Infect. Control. 2014; 3: 35. DOI: 10.1186/2047-2994-3-35.
19. Yang J., Xue W., Yu X. Elizabethkingia meningosepticum endocarditis: A rare case and special therapy. Anatol. J. Cardiol. 2015; 15: 427. DOI: 10.5152/akd.2015.6014.
20. Chi S., Fekete T. Epididymo-orchitis. In: Schlossberg D., editor. Clinical Infectious Disease. 2nd ed. Cambridge University Press; Cambridge, UK. 2015: 401–5.
21. Gonzalez C., Coolen-Allou N., Allyn J. et al. Severe sepsis and pulmonary abscess with bacteremia due to Elizabethkingia miricola. Med. Mal. Infect. 2015; 46: 49–51. DOI: 10.1016/j.medmal.2015.10.011.
22. aufiq Kadafi K., Yuliarto S., Aji Cahyono H. et al. Cerebral Salt Wasting Due to Bacteremia Caused by Elizabethkingia meningoseptica: A Case Report. Arch. Pediatr. Infect. Dis. 2020; 8: e44832. DOI: 10.5812/pedinfect.88432.
23. Kenna D.T., Fuller A., Martin K. et al. rpoB gene sequencing highlights the prevalence of an E. miricola cluster over other Elizabethkingia species among UK cystic fibrosis patients. Diagn. Microbiol. Infect. Dis. 2018; 90: 109–14. DOI: 10.1016/j.diagmicrobio.2017.10.014.
24. Amir A., IC Sam J., Nawi S. Elizabethkingia meningoseptica neonatal meningitis in a premature infant. Asian J. Med. Biomed. 2018; 2(Suppl. 1): 22.

25. Seong H., Kim J.H., Kim J.H. et al. Risk factors for mortality in patients with elizabethkingia infection and the clinical impact of the antimicrobial susceptibility patterns of elizabethkingia species. J. Clin. Med. 2020; 9: 1431. DOI: 10.3390/jcm9051431.
26. Nori P., Cowman K., Chen V. et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect. Control Hosp. Epidemiol. 2021; 42: 84–8. DOI: 10.1017/ice.2020.368.
27. Yang C., Liu Z., Yu S. et al. Comparison of three species of Elizabethkingia genus by whole-genome sequence analysis. FEMS Microbiol. Lett. 2021; 368: fnab018. DOI: 10.1093/femsle/fnab018.
28. King E.O. Studies on a group of previously unclassified bacteria associated with meningitis in infants. Am. J. Clin. Pathol. 1959; 31: 241–7. DOI: 10.1093/ajcp/31.3.241.
29. Nicholson A.C., Gulvik C.A., Whitney A.M. et al. Revisiting the taxonomy of the genus Elizabethkingia using whole-genome sequencing, optical mapping, and MALDI-TOF, along with proposal of three novel Elizabethkingia species: Elizabethkingia bruuniana sp. nov., Elizabethkingia ursingii sp. nov., and Elizabethkingia occulta sp. nov. Antonie Van Leeuwenhoek. 2018; 111: 55–72. DOI: 10.1007/s10482-017-0926-3.
30. Hwang J.-H., Kim J., Kim J.-H., Mo S. Elizabethkingia argenteiflava sp. nov., isolated from the pod of soybean, Glycine max. Int. J. Syst. Evol. Microbiol. 2021; 71: 004767. DOI: 10.1099/ijsem.0.004767.
31. Hem S., Jarocki V.M., Baker D.J. et al. Genomic analysis of Elizabethkingia species from aquatic environments: Evidence for potential clinical transmission. Curr. Res. Microb. Sci. 2022; 3: 100083. DOI: 10.1016/j.crmicr.2021.100083.
32. Zajmi A., Teo J., Yeo C.C. Epidemiology and Characteristics of Elizabethkingia spp. Infections in Southeast Asia. Microorganisms. 2022; 10(5): 882. DOI: 10.3390/microorganisms10050882. PMID: 35630327; PMCID: PMC9144721.
33. Breurec S., Criscuolo A., Diancourt L. et al. Genomic epidemiology and global diversity of the emerging bacterial pathogen Elizabethkingia anophelis. Sci. Rep. 2016; 6: 30379. DOI: 10.1038/srep30379.
34. Lin J.-N., Lai C.-H., Yang C.-H., Huang Y.-H. Elizabethkingia infections in humans: From genomics to clinics. Microorganisms. 2019; 7: 295. DOI: 10.3390/microorganisms7090295.
35. Kwambana-Adams B., Laxton C., Foster-Nyarko E. et al. Isolation of Methicillin-resistant Staphylococcus aureus and Multidrug-resistant Elizabethkingia meningoseptica from Neonates within Minutes of Birth. Pediatric Infect. Dis. J. 2017; 36: 123–4. DOI: 10.1097/INF.0000000000001368.
36. Huang Y., Huang Y., Lin Y. et al. Risk factors and outcome of levofloxacin-resistant Elizabethkingia meningoseptica bacteraemia in adult patients in Taiwan. Eur. J. Clin. Microbiol. Infect. Dis. 2017; 36: 1–8. DOI: 10.1007/s10096-017-2942-7.

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PATIENT WITH COSTELLO SYNDROME: LITERATURE REVIEW AND CLINICAL CASE

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Abstract. Costello syndrome belongs to RAS-pathies and is a multisystem disease based on a heterozygous mutation of the HRAS gene. Frequent characteristic features are a specific phenotype with dysmorphic facial features, delayed mental and psychomotor development, and a tendency to develop neoplasms. The biphasic growth of patients with the development of severe nutritional deficiency after birth causes difficulties in correction of a trophological status. A large number of diseases included in the range of differential diagnosis can cause difficulties in early diagnosis and adequate therapy because of polymorphism of the clinical picture of the disease. The article provides a literature review devoted to the analysis of the mechanisms of development of Costello syndrome, as well as a 4-year observation of a patient whose clinical picture consisted of mental retardation, impaired psychomotor and physical development, severe protein-energy malnutrition, dermatological complications, as well as the development of embryonal rhabdomyosarcoma of the bladder.

Key words: *Costello syndrome; developmental delay; embryonal rhabdomyosarcoma; nutritional status.*

ПАЦИЕНТ С СИНДРОМОМ КОСТЕЛЛО: ОБЗОР ЛИТЕРАТУРЫ И КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. Синдром Костелло относится к RAS-патиям и представляет собой полисистемное заболевание, в основе которого лежит гетерозиготная мутация гена *HRAS*. Частыми характерными особенностями является специфический фенотип с дисморфорическими чертами лица, задержка умственного и психомоторного развития, склонность к развитию новообразований. Двухфазный рост пациентов с развитием после рождения выраженного нутритивного дефицита вызывает трудности в коррекции трофологического статуса. Широкий спектр заболеваний, входящий в круг дифференциальной диагностики при полиморфизме клинической картины заболевания, может вызвать затруднения в ранней диагностике и проведении адекватной терапии. В статье приводится обзор литературы, посвященный анализу механизмов развития синдрома Костелло, а также 4-летнее наблюдение за пациентом, клиническая картина которого заключалась в умственной отсталости, нарушении психомоторного и физического развития, выраженной белково-энергетической недостаточности, дерматологических осложнениях, а также развитии эмбриональной рабдомиосаркомы мочевого пузыря.

Ключевые слова: *синдром Костелло; задержка развития; эмбриональная рабдомиосаркома; нутритивный статус.*

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EPIDEMIOLOGY AND PATHOGENESIS

Costello syndrome (OMIM No. 218040) is a unique case of RAS-pathies (retrovirus associated sequences) and a rare polysystemic disease, which is caused by a heterozygous mutation in the *HRAS* gene (190020) on chromosome 11p15. 5. It is characterized by dysmorphic facial features, biphasic growth, motor and mental retardation, ectodermal dysplasia, papillomas. There are also pathological changes in the cardiovascular, endocrine, nervous, and digestive systems, and increased susceptibility to cancer. The mutation of the HRAS gene, which normally encodes guanosine triphosphatase (GTPase), leads to changes in the cascade of mitogen-activated protein kinases (MARK), which determine fundamental biological functions such as cell proliferation, differentiation, and Its survival [1–3].

Costello syndrome (CS) is a rare disease with autosomal dominant de novo mutations with an incidence in live births ranging from 1:300,000 to 1:24,000,000 [4–6]. There is a prenatal large fetus development with subsequent lag in postnatal physical development [7]. A growth retardation is determined by nutritional deficiencies due to feeding difficulties. In 1971, at first, and then in 1977 New Zealand pediatrician Jack Costello described two unrelated children with the syndrome, which included short stature, mental retardation, skin manifestations in the form of excessive skin on the neck, palms, soles of feet and fingers with hyperkeratosis, curly thin hair, papillomas [8, 9].

The main pathogenetic pathways of CS are impaired formation of elastic fibers due to low production of tropoelastin and microfibrillar proteins, its inadequate secretion and extracellular assembly [10]. A. Hinek et al. described causes of CS development in 6 children with confirmed diagnosis. Scientists determined that fibroblasts produced normal levels of soluble tropoelastin, but they were unable to assemble elastic fibers due to secondary deficiency of elastin-binding protein (EBP) [10]. Because the normal association between tropoelastin and EBP can be damaged by contact with fragments containing galactose, and accumulation of chondroitin sulfate-containing proteoglycans and biglycan was noted in fibroblasts from CS patients, it was hypothesized that chondroitin sulfate can induce the release of ESB from cells and prevent normal recycling of reusable tropoelastin chaperone [10, 11].

Correlations between genotype changes and corresponding phenotypic features were proved [12]. Patients with HRAS mutation and Costello syndrome more often have polyuria, ulnar deviation, growth hormone deficiency and tachycardia, than patients with *BRAF* or *MEK1* mutations [13]. Moreover, patients with *G13C* alterations also show polymorphism (polyhydramnios, macrocephaly, delayed physical and mental development, hypertrophic cardiomyopathy, and posterior fossa crowding) in clinical picture [14]. However, patients with *p.G12A* or *p.G12C HRAS* alteration have more severe phenotypic and morphofunctional manifestations than patients with other *HRAS* mutations [15]. Regardless of the mutation, severity did not significantly increase over time. Almost all of literature sources shows that there is no specific therapy for CS. The symptomatic treatment is used in therapy of CS. The treatment is aimed at nutritional support, prevention and therapy of emerging cardiac, gastrointestinal, and respiratory disorders.

The appearance of papillomas has been noted in children mainly on the face (a projection of the nasolabial triangle) and perianal area [16–18]. A mental retardation in various extents is an important diagnostic and sometimes prognostic factor in the structure of CS [19]. Children with CS are more susceptible to the development of autism spectrum disorders, especially children of 2–4 years old [20, 21]. The cause of CS development is associated with mutations in the HRAS gene, but it was found that patients may show signs of cardio-facio-cutaneous syndrome (CFC), and also referred to RAS-pathies [22, 23].

Di Rocco et al. were the first who wrote about oral-motor apraxia and associated malnutrition in patients with CS [24]. The case analysis showed marasmus-type of growth chart changes in the postnatal period in the majority of SC patients [4, 25, 26]. S. Umans et al. described a case of oropharyngeal dysphagia in the structure of CS [27]. The concomitant cause of trophoblastic deficiency was a severe gastroesophageal reflux disease in some patients [28]. In addition, a tendency to stomach and duodenum ulcerative process was described [29]. Problems of patient feeding and the need for artificial feeding with high-calorie formulas through a tube are posed by H. Kawame [30]. The dysphagia syndrome usually resolves in 4-yaers old children with CS [9, 31].

Clinical forms of CS with cardiovascular pathology, specifically rhythm disturbances and extrasystoles, as well as mitral valves thickening, pulmonary artery stenosis or hypertrophic cardi-

omyopathy, were described [32–34]. Therefore, the routine follow-up of cardiovascular system is recommended for all patients with CS.

A growth retardation in these patients is often associated with growth hormone deficiency [35]. Decreased cortisol concentrations and hypoglycemia also was noted [36–38].

An increased risk of malignant neoplasms, mainly in muscle tissues, was observed in patients with CS [39]. Thus, M. Feingold et al. reported about a child with confirmed CS who had alveolar rhabdomyosarcoma of the right foot which appeared in infancy [40]. B. Kerr et al. not only reported about two children with CS, who developed retroperitoneal embryonal rhabdomyosarcoma in infancy, but also associated an increased risk of malignization as a structural part of Costello syndrome [41]. K.W. Gripp et al. in 2002 also described 5 cases of abdominal, pelvic or urogenital rhabdomyosarcoma in patients with CS [42]. The literature review shows that all patients with CS and *p.Gly12Ser* or *p.Gly12Ala* genotype variants developed cancer [14, 43]. An intrathoracic ganglioneuroblastoma and bladder carcinoma were also detected in children with CS [44–46].

The issues of prenatal diagnosis have not been developed because the syndrome is rare, as well as the lack of specific signs of fetal phenotype was found [47, 48].

CLINICAL CASE

We present our own 4-year observation of a patient with Costello syndrome. The typical course of CS included in addition to mental retardation, disorders of psychomotor and physical development, marked malnutrition, and dermatologic manifestations, was accompanied by embryonal rhabdomyosarcoma of the bladder. Its surgical treatment leaded to recurrent vesico-uretero-renal reflux.

Patient M., born in 2015, was observed in the clinic from January 2019 to November 2022. At first he was admitted to the hospital at the age of 3 years 11 months in a serious condition with complaints of recurrent urinary tract infections, which have developed because of a pelvic and abdominal neoplasm compressing the left ureter. It was complicated with the ureterohydronephrosis on the left side. The accompanying diagnosis was Costello syndrome. The patient was transferred from a multidisciplinary hospital for left ureter stenting as part of preoperative preparation.

Anamnesis vitae. The child from the fourth pregnancy, which was without complications, second childbirth at 37 weeks (1 — medical abortion; 2 — healthy premature boy 3700 g, 53 cm, then he was a healthy child, 3 — missed abortion at 8/9 weeks). No fetal pathology was detected by prenatal testing. The birth weight was 4750 g (7^{th}-centile corridor (c.c.), Z-score — 2.55). The birth length was 54 cm (7^{th} c.c., Z-score — 2.17). An Apgar score was 7/8 points. The child's parents were healthy; they did not have any chronic somatic or diagnosed hereditary diseases. The marriage was unrelated.

A pseudobulbar syndrome and motor disorders were diagnosed in the early neonatal period. Multiple small developmental anomalies (keel-shaped deformation of the chest, macrocephaly, wide nose bridge, face with a large mouth, thick lips, skin folds, large forehead) were revealed.

On the examination, there was a disproportionate enlargement of hands and feet to the extremities. A right clavicle fracture, early neonatal hypoglycemia, and hepatosplenomegaly were diagnosed.

On the 2^{nd} day of life, a hyperbilirubinemia 249 μmol/L was detected (the direct fraction was 238 μmol/L); a differential diagnosis was made with mucopolysaccharidosis and Sotos syndrome (subsequently excluded). At the age of 1 month, a routine neurosonography revealed triventriculodilatation, enlargement of subarachnoid spaces, hypogenesis of the corpus callosum, hypoplasia of the cerebellar vermis, and enlargement of the cisterna magna.

The breastfeeding was until 2 months and then due to weakness of sucking and swallowing reflexes he was transferred to tube feeding. Then, pronounced psychomotor development delays were found. The child walks with help since 2 years of age. He had a delayed psycho-verbal development. He cannot be sitting or standing independently.

In the view of the suspicion of genetic disease, karyotyping and HRAS gene sequencing were performed. A karyotype 46XY and a partial *de novo* missense mutation in codon 12c.35G>A (*p.Gly12Ala*) in heterozygous state was detected. Thus, Costello syndrome was diagnosed.

During the first year he grew 3 cm (57 cm — 1 c.c., Z-score — –7.87), weight gain was 1.5 kg (6.25 kg, 1 c.c., Z-score — –3.82). A nocturnal alimentation via nasogastric tube was performed

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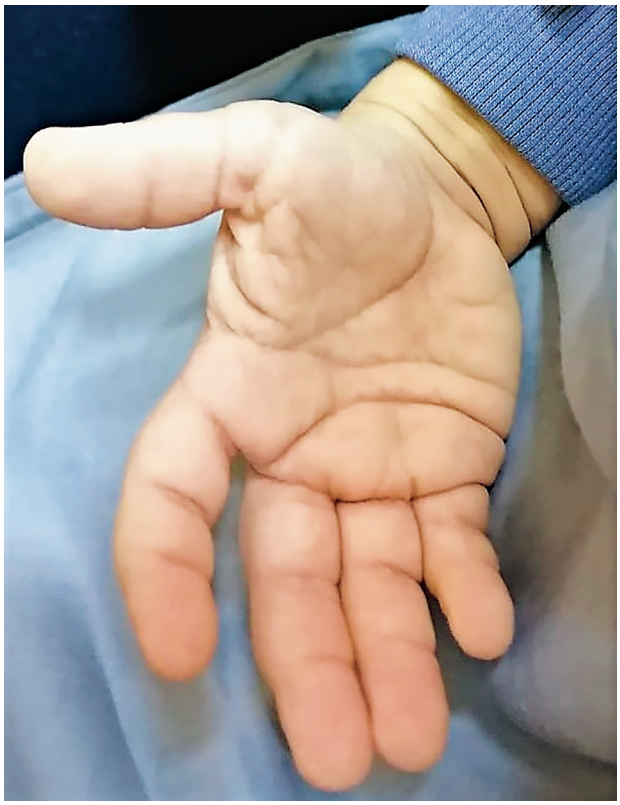


Fig. 1. Patient's palms (own observation)
Рис. 1. Ладони пациента (собственное наблюдение)

until 1.5 years of age on the recommendation of a nutritionist.

The allergoanamnesis is not aggravated. A prophylactic vaccination before the debut of the disease according to an individual calendar was with a delay. Past diseases: upper respiratory tract infections. Traumas were not noted. The main disease is not observed by a geneticist.

Anamnesis morbi

At the age of 3 years 11 months, the mother independently noticed a mass in the lower part of the abdomen, and because of that the child was taken to a children's specialized multidisciplinary hospital by an ambulance. During ultrasound examination of the abdominal cavity, kidneys and urinary tract organs (03.01.2018): a formation in the pelvis, pyelectasis on the left, enlargement of the ureter on the left were detected. In this way, the child underwent multispiral computed tomography of the abdominal cavity, retroperitoneum and pelvis. The results revealed a CT picture of space-occupying lesion with possible invasion of *m. psoas* on the left, pronounced volumetric impact, signs of hydronephrosis on the left against the background of compression of the left ureter. On 05.01.2019 laboratory determined the increase in the concentration of neuron-specific enolase (NSE) — 39.8 mcg/l (normal level is less than 18.3 mcg/l). The excretion of catecholamine metabolites in the urine on 05.01.2019 — the result was normal. On 09.01.2019, for the purpose of differential diagnosis, an incisional biopsy of pelvic mass, bone marrow aspiration from 4 points, bone marrow trepanobiopsy from 2 points were performed. Pathomorphologically, the embryonal rhabdomyosarcoma of the bladder was diagnosed. There were no pathologic changes in the bone marrow. In the view of the compression of the left ureter, its stenting was recommended. In January 2019, the child was admitted to the surgical department of the clinic for ureter stenting on the left.

Objectively on admission: the patient's condition was serious due to the disease, a consciousness was clear, intelligence was decreased, the patient was friendly, willingly made contact. In the neurological picture there were not any focal neurological signs, severe delay in psychomotor and verbal development, nystagmus.

Multiple developmental anomalies of the musculoskeletal apparatus were revealed: deformation of the thorax and limbs, hydrocephalic form of the skull. The subcutaneous fat was sharply reduced; the patient has a muscle hypotonia. A nasal breathing was difficult. Heart tones were rhythmic, loud. The patient had a tendency to constipations. Phenotypic changes of the palms, characteristic for CS patients and shown in the literature, were also noted in the patient (Fig. 1) [14]. Perianal papillomas were detected.

During the preoperative check-up in 2019, the results of ultrasound examination revealed a mass in pelvic and abdominal cavity, the kidney's size was in accordance with the age norm (the right was 73.9×29.1 mm, parenchyma — 11.7 mm, pelvicalyceal system is not dilated; the left kidney — 81.2×33.7 mm, an anteroposterior diameter of the pelvic — 28.2×28.3 mm, parenchyma — 9 mm), dilation of the left ureter in the distal 1/3 was 7.2 mm. NSE values (15.01.2019) were 369.5 ng/mL. On 17.01.2019, surgical ureter stenting on the left was performed. The control ultrasound detected, that the left kidney pelvic was 18×18 mm, parenchyma — 8 mm, the left ureter in the distal 1/3 dilated to 7 mm. Then, the child was transferred to the urological department of the Children's Oncology Center for treatment of oncological disease.

After 9 courses of targeted polychemotherapy, on 24.02.2019, the child underwent radical surgery: laparotomy, cystotomy, bladder tumor removal with resection of the distal 1/3 of the left ureter, ureterocystoneoanastomosis, cystostomy; a biopsy of the subcapsular formation of the left kidney, drainage of the abdominal cavity was done. In the early postoperative period, a course of polychemotherapy (PCT) was started according to the CWS-2009 protocol. The histologic conclusion was: embryonal rhabdomyosarcoma with signs of maturation, post-therapeutic changes, first degree.

On the next hospitalization on 11.09.2019, the removal of the internal ureteral stent on the left was performed. Urodynamic disorders and recurrent urinary tract infections were not detected.

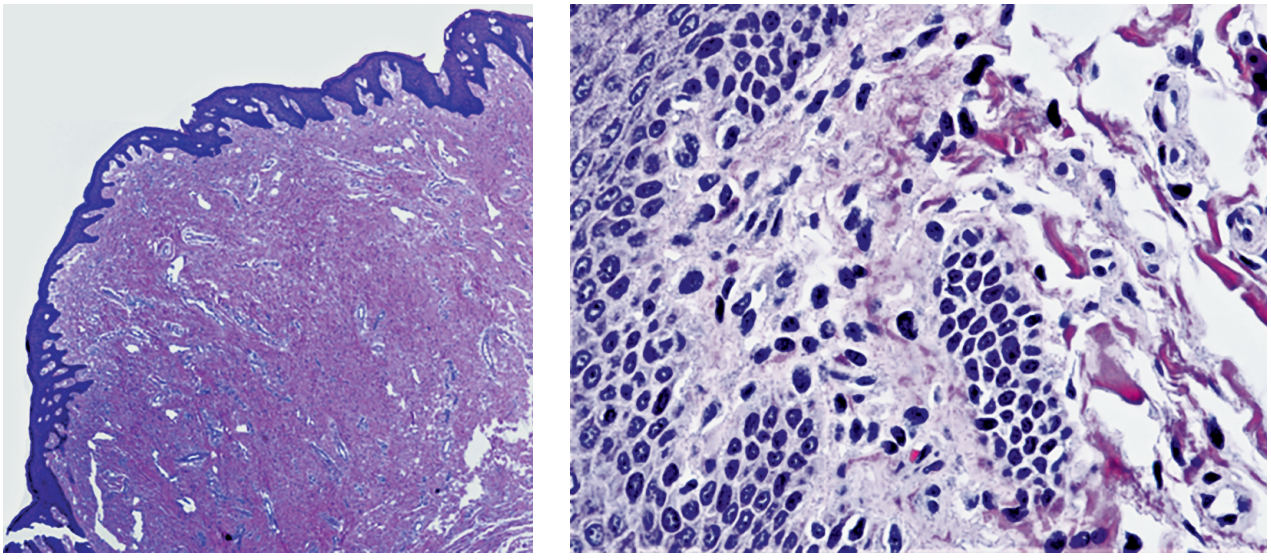
In the period from 17.10.2019 to 26.11.2019, a course of proton radiation therapy was performed on the area of the original tumor and the postoperative pelvic tumor place with a margin for micro-proliferation followed by local boost on the area of residual tissue of the formation.

According to the results of control cystography on 07.06.2020, vesico-uretero reflux (VUR) on the left (III degree) was still presented. Because of that endoscopic treatment of left VUR (endoscopic gel injection of the left ureterovesical junction) was performed on 19.06.2020. According to the results of a control cystography, the left VUR of III degree was detected, the control ultrasound of kidneys and bladder showed a decrease in the size of the left kidney with enlargement of the renal pelvis 19.60×37.9 mm. In this regard, on 23.03.2021, the next endoscopic treatment of left VUR was performed. The laser removal of perianal papillomas was performed (according to the results of histologic study — keratin masses and strata of multilayer squamous epithelium without vacuolar degeneration, with artificial changes without underlying stroma) (Fig. 2).

Immunohistochemical examination for human papillomaviruses did not show expression in the multilayer squamous epithelium. The postoperative period proceeded without complications. There were no signs of acute disturbance of urodynamics at ultrasound control. On 27.10.2021 a control cystography was performed: VRU of III degree on the left side was revealed. An endoscopic treatment of the left VRU was repeatedly performed.

At age of 5 years, his height was 71 cm (Z-score — -8.55), weight — 7.9 kg (Z-score — –5.63), BMI — 15.7 (27.4th percentile).

On 25.11.2021 MRI of abdominal cavity organs, retroperitoneal organs with contrasting was performed to determine further tactics: the condition after surgical treatment of embryonal radbomyosarcoma of the bladder, PCT was noted without significant dynamics, no active accumulation of contrast agent. The interpretation of changes in the left kidney was the same. The deformation of the bladder was detected.



А/A В/Б

Fig. 2: Histologic study of skin biopsy: A — magnification ×40; B — magnification ×400. Hematoxylin and eosin staining

Рис. 2. Гистологическое исследование биоптата кожи: А — увеличение ×40; Б — увеличение ×400. Окраска гематоксилином и эозином

The patient was re-examined by nutritionists and pediatricians during routine hospitalization at the age of 7 years. Body weight was 16 kg (1 c.c.). Objectively, there were also signs of severe malnutrition (sharp decrease in the development of the subcutaneous fat, decreased tissue turgor), multiple developmental anomalies, limb deformities, dysmorphic facial features, changes in palms, soles of feet and fingers with hyperkeratosis.

During the hospitalizations, no abnormalities were detected according to the data of control electrocardiographic and echocardiographic studies.

On 01.11.2022, the micturition cystography revealed VRU of III-IV degree on the left, rounded bladder with smooth contours. According to the results of ultrasound of kidneys and bladder, there were nephrosclerosis of the left kidney (57.1×26.9 mm), thinning of parenchyma — 9.3 mm; the right kidney has a normal size.

During dynamic renal scintigraphy (RSG): morphologicaly the parenchyma of the right kidney had a normal function, the left kidney had not any function activity. According to MRI of the abdominal cavity and retroperitoneum performed in November 2022, the left kidney was reduced (27×27×59 mm), represented by multicystic structures, the contours are uneven, corticomedullar differentiation was not traced, the left renal pelvis was moderately dilated, the ureter had a different diameter, multiple small cystic inclusions ~1–3 mm in diameter were traced in the distal part of the ureter wall. No zones of active pathologic accumulation were noted during contrasting. Lymph nodes were visualized in the pararenal space on the left side with the size 3.5 mm. In the retroperitoneal space on the left, paravertebrally at the level of Th XI-L I, there are nodular areas along the course of renal vessels on the left with clear contours, shape and size ~22×10×44 mm, which enveloped the renal vessels in a "muff-like" way. No evidence for restriction of diffusion was obtained. After contrast agent injection no zones of active accumulation in the foci were noted. The bladder was deformed in the bottom area, pulled to the left in the projection of the deformed left ureter, no zones of pathologic contrasting were noted. The right kidney was located normally, its size was ~42×42×80 mm, corticomedullar differentiation was not disturbed. The kidney contours were smooth. There was no evidence of the right kidney pelvicalyceal system enlargement. The pararenal space was not compacted. The adrenal glands were traced on both sides. Their shape and size were preserved. No pathologic formations in their structure were revealed.

DISCUSSION

This article presents a rare case of long-term observation of Costello syndrome caused by partial *de novo* missense mutation in codon 12 c.35G>A (*p.Gly12Ala*). The leading phenotypic manifestations of the syndrome were mental retardation, delayed psychomotor development, biphasic growth (large fetal size for gestational age followed by postnatal reduction of development), pronounced malnutrition with dysphagia, macrocephaly, development of neoplasms, dysmorphic signs on the face, typical skin signs and papillomas. Child's physical and neuropsychiatric development was delayed.

The CS of p.G12A phenotype is the second most common missense mutation with a high malignancy rate [12]. In the case, the patient had embryonal rhabdomyosarcoma of the bladder in the period of the second childhood. Surgical treatment of oncologic disease with partial resection of the left ureter and anastomosis resulted in the vesicoureteral reflux of III-IV degree, which was resistant to surgical treatment, with subsequent nephrosclerosis and multicystic transformation of the left kidney. Early oncologic disease may indicate the degree of HRAS proto-oncogene activity.

In addition to malignant neoplasms, the patient was also found to have benign papillomas unrelated to human papillomavirus, which is the result of a mutation in the HRAS proto-oncogene [17, 33, 47]. Their features were perianal localization (rarer than nasal papillomas) and later manifestation — at the age of 4 years (previously encountered from birth to 2–3 years) [8].

The long-term survival of the patient was due to normalization of nutrition and elemination of the malnutrition. A dysphagia in the structure of pseudobulbar syndrome was noted early. It required not only transfer to artificial feeding, but also the use of a nocturnal alimentation regimen. At the age of 4-5 years, the clinical picture of dysphagia regressed, which allowed to normalize an enteral nutrition.

CONCLUSION

The case report of a 4-year follow-up of Costello syndrome of the boy with embryonal rhabdomyosarcoma of the bladder shows the need for

caution in cancer in children with diagnosed CS. The lack of reliable criteria for prenatal ultrasound diagnosis determines the difficulties in making the diagnosis before birth. An elimination of malnutrition, which develops in children with CS and associated with pathology both digestive and nervous systems, is an important therapeutic goal.

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, fi nal approval of the version to be published and agree to be accountable for all aspects of the study.

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

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Informed consent. The informed consent on publication of patient's data from patient's parents was not received. All the provided information in this article is impersonal, any identifying information has been deleted.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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REFERENCES

1. Gabitova N.Kh., Kazakova F.M., Khakimova R.N. Sluchay redkogo zabolevaniya u novorozhdennogo rebenka. [The case of rare diseases at the newborn child]. Prakticheskaya meditsina. 2012; 9(65): 185–7. (In Russian).
2. Karnoub A.E., Weinberg R.A. Ras oncogenes: split personalities. Nature reviews. Molecular cell biology. 2008; 9(7): 517–31. DOI: 10.1038/nrm2438.
3. Dard L., Hubert C., Esteves P. et al. HRAS germline mutations impair LKB1/AMPK signaling and mitochondrial homeostasis in Costello syndrome models. The Journal of clinical investigation. 2022; 132(8): e131053. DOI: 10.1172/JCI131053.
4. Vasina T.N., Zubtsova T.I., Stavtseva S.N. i dr. Klinicheskaya diagnostika redkogo nasledstvennogo zabolevaniya — sindroma Kostello. [Clinical diagnosis of a rare hereditary disease — Costello's syndrome]. Rossiyskiy vestnik perinatologii i pediatrii. 2010; 5: 27–30. (In Russian).
5. Vurallia D., Kosukcub C., Taskiranb E. et al. Hyperinsulinemic hypoglycemia in a patient with Costello syndrome: an etiology to consider in hypoglycemia. Molecular syndromology. 2020; 11: 207–16. DOI: 10.1159/000510171.
6. Aoki Y., Niihori T., Kawame H. et al. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nature genetics. 2005; 37: 1038–40. DOI: 10.1038/ng1641.
7. Kharitonova N.A., Basargina M.A., Mitish M.D. i dr. Sindrom Kostello v praktike neonatologa. Klinicheskiy sluchay. [Costello syndrome in the practice of a neonatologist. A clinical case.]. Meditsinskiy opponent. 2021; 4(16): 76–80. (in Russian).
8. Costello J.M. A new syndrome: mental subnormality and nasal papillomata. Australian paediatric journal. 1977; 13: 114–8. DOI: 10.1111/j.1440-1754.1977.tb01135.x.
9. Peixoto I.L., Carreno A.M., Prazeres V.M. et al. Syndrome in question. Costello syndrome. Anais brasileiros de dermatologia. 2014; 89(6): 1005–6. DOI: 10.1590/abd1806-4841.20143062.
10. Hinek A., Teitell M.A., Schoyer L., et al. Myocardial storage of chondroitin sulfate-containing moieties in Costello syndrome patients with severe hypertrophic cardiomyopathy. American journal of medical genetics. 2005; 133A(1): 1–12. DOI: 10.1002/ajmg.a.30495.
11. Privitera S., Prody C.A., Callahan J.W. et al. The 67-kDa enzymatically inactive alternatively spliced variant of beta-galactosidase is identical to the elastin/laminin-binding protein. The Journal of

biological chemistry. 1998; 273(11): 6319–26. DOI: 10.1074/jbc.273.11.6319.
12. Gripp K.W., Morse L.A., Axelrad M. et al. Costello syndrome: Clinical phenotype, genotype, and management guidelines. American journal of medical genetics. 2019; 179(9): 1725–44. DOI: 10.1002/ajmg.a.61270.
13. Gripp K.W., Lin A.E., Nicholson L. et al. Further delineation of the phenotype resulting from BRAF or MEK1 germline mutations helps differentiate cardio-facio-cutaneous syndrome from Costello syndrome. American journal of medical genetics. 2007; 143A: 1472–80. DOI: 10.1002/ajmg.a.31815.
14. Gripp K.W., Hopkins E., Sol-Church K. et al. Phenotypic analysis of individuals with Costello syndrome due to HRAS p.G13C. American journal of medical genetics. 2011; 155A: 706–16. DOI: 10.1002/ajmg.a.33884.
15. McCormick E.M., Hopkins E., Conway L. et al. Assessing genotype-phenotype correlation in Costello syndrome using a severity score. Genetics in medicine: official journal of the American College of Medical Genetics. 2013; 15: 554–7. DOI: 10.1038/gim.2013.6.
16. Kerr B., Delrue M.-A., Sigaudy S. et al. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. Journal of medical genetics. 2006; 43: 401–5. DOI: 10.1136/jmg.2005.040352.
17. Martin R.A., Jones K.L. Delineation of the Costello syndrome. American journal of medical genetics. 1991; 41: 346–9. DOI: 10.1002/ajmg.1320410316.
18. Der Kaloustian V.M., Moroz B., McIntosh N. et al. Costello syndrome. American journal of medical genetics. 1991; 41: 69–73. DOI: 10.1002/ajmg.1320410118.
19. Okamoto N., Chiyo H., Imai K. et al. A Japanese patient with the Costello syndrome. Human genetics. 1994; 93: 605–6. DOI: 10.1007/BF00202834.
20. Schwartz D.D., Katzenstein J.M., Highley E.J. et al. Age-related differences in prevalence of autism spectrum disorder symptoms in children and adolescents with Costello syndrome. American journal of medical genetics. 2017; Part A, 173(5): 1294–1300. DOI: 10.1002/ajmg.a.38174.
21. Young O., Perati S., Weiss L.A. et al. Age and ASD symptoms in Costello syndrome. American journal of medical genetics. 2018; Part A, 176(4): 1027–8. DOI: 10.1002/ajmg.a.38641.
22. Leoni C., Romeo D.M., Pelliccioni M. et al. Musculo-skeletal phenotype of Costello syndrome and cardio-facio-cutaneous syndrome: insights on the functional assessment status. Orphanet journal of rare diseases. 2021; 16(1): 43. DOI: 10.1186/s13023-021-01674-y.
23. Qian W., Zhang M., Huang H. et al. Costello syndrome with special cutaneous manifestations and HRAS G12D mutation: A case report and literature review. Molecular genetics & genomic medicine. 2021; 9(6): e1690. DOI: 10.1002/mgg3.1690.
24. Di Rocco M., Gatti R., Gandullia P. et al. Report on two patients with Costello syndrome and sialuria. American journal of medical genetics. 1993; 47(7): 1135–40. DOI: 10.1002/ajmg.1320470737.
25. Gripp K.W., Rauen K.A. Costello syndrome. Gene Reviews. 2020: 1–29.
26. Zampino G., Pantaleoni F., Carta C. et al. Diversity, parental germline origin, and phenotypic spectrum of de novo HRAS missense changes in Costello syndrome. Human mutation. 2007; 28(3): 265–72. DOI: 10.1002/humu.20431.
27. Umans S., Decock P., Fryns J.P. Costello syndrome: the natural history of a true postnatal growth retardation syndrome. Genetic counseling. 1995; 6(2): 121–5.
28. Fryns J.P., Vogels A., Haegeman J. et al. Costello syndrome: a postnatal growth retardation syndrome with distinct phenotype. Genetic counseling. 1994; 5(4): 337–43.
29. Costello J.M. Costello syndrome: update on the original cases and commentary. (Letter). American journal of medical genetics. 1996; 62(2): 199–201. DOI: 10.1002/ajmg.1320620203.
30. Kawame H., Matsui M., Kurosawa K. et al. Further delineation of the behavioral and neurologic features in Costello syndrome. American journal of medical genetics. 2003; 118A(1): 8–14. DOI: 10.1002/ajmg.a.10236.
31. Leoni C., Giorgio V., Onesimo R. et al. Impact of Costello syndrome on growth patterns. Am American journal of medical genetics. 2020; Part A, 182(11): 2797–9. DOI: 10.1002/ajmg.a.61812.
32. Ishida S., Mutsuga M., Fujita T. et al. Surgical techniques for infectious endocarditis of the mitral valve with hypertrophic cardiomyopathy in Costello syndrome. Journal of cardiology cases. 2022; 25(6): 367–9. DOI: 10.1016/j.jccase.2021.12.010.
33. Lin A.E., Rauen K.A., Gripp K.W. et al. Clarification of previously reported Costello syndrome patients. (Letter). American journal of medical genetics. 2008; Part A, 146A(7): 940–3. DOI: 10.1002/ajmg.a.32164.
34. Smith L.P., Podraza J., Proud V.K. Polyhydramnios, fetal overgrowth, and macrocephaly: prenatal ultrasound findings of Costello syndrome. American

journal of medical genetics. 2009; Part A, 149A(4): 779–84. DOI: 10.1002/ajmg.a.32778.
35. Torrelo A., Lopez-Avila A., Mediero I.G. et al. Costello syndrome. Journal of the American Academy of Dermatology. 1995; 32(5 Pt 2): 904–7. DOI: 10.1016/0190-9622(95)91559-1.
36. Gripp K.W., Lin A.E. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from HRAS germline mutations. Genetics in medicine: official journal of the American College of Medical Genetics. 2012; 14(3): 285–92. DOI: 10.1038/gim.0b013e31822dd91f.
37. Leoni C., Flex E. Costello Syndrome: The Challenge of Hypoglycemia and Failure to Thrive. EBioMedicine. 2018; 27: 5–6. DOI: 10.1016/j.ebiom.2017.12.006.
38. Leoni C., Onesimo R., Giorgio V. et al. Understanding growth failure in Costello syndrome: increased resting energy expenditure. The Journal of pediatrics. 2016; 170: 322–4. DOI: 10.1016/j.jpeds.2015.11.076.
39. Sánchez-Montenegro C., Vilanova-Sánchez A., Barrena-Delfa S. et al. Costello Syndrome and Umbilical Ligament Rhabdomyosarcoma in Two Pediatric Patients: Case Reports and Review of the Literature. Case reports in genetics. 2017: 1587610. DOI: 10.1155/2017/1587610.
40. Feingold M. Costello syndrome and rhabdomyosarcoma. (Letter). Journal of medical genetics. 1999; 36(7): 582–3.
41. Kerr B., Eden O.B., Dandamudi R. et al. Costello syndrome: two cases with embryonal rhabdomyosarcoma. Journal of medical genetics. 1998; 35(12): 1036–9. DOI: 10.1136/jmg.35.12.1036
42. Gripp K.W., Scott C.I., Nicholson L. et al. Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. American journal of medical genetics. 2002; 10(1): 80–7. DOI: 10.1002/ajmg.10241.
43. Menke J., Pauli S., Sigler M. et al. Uniparental trisomy of a mutated HRAS proto-oncogene in embryonal rhabdomyosarcoma of a patient with Costello syndrome. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(13): e62–5. DOI: 10.1200/JCO.2013.49.6539.
44. Moroni I., Bedeschi F., Luksch R. et al. Costello syndrome: a cancer predisposing syndrome? Clinical dysmorphology. 2000; 9(4), 265–8. DOI: 10.1097/00019605-200009040-00006.
45. Franceschini P., Licata D., Di Cara G. et al. Bladder carcinoma in Costello syndrome: report on a patient born to consanguineous parents and review. American journal of medical genetics. 1999; 86(2): 174–9.
46. Gripp K.W., Scott C.I., Nicholson L. et al. Second case of bladder carcinoma in a patient with Costello syndrome. (Letter). American journal of medical genetics. 2000; 90(3): 256–9. DOI: 10.1002/(sici)1096-8628(20000131)90:3<256::aid-ajmg16>3.0.co;2-d.
47. Lin A.E., O'Brien B., Demmer L.A. et al. Prenatal features of Costello syndrome: ultrasonographic fndings and atrial tachycardia. Prenatal diagnosis. 2009; 29(7): 682–90. DOI: 10.1002/pd.2276.
48. Leoni C., Viscogliosi G., Tartaglia M. et al. Multidisciplinary Management of Costello Syndrome: Current Perspectives. Journal of multidisciplinary healthcare. 2022; 15: 1277–96. DOI: 10.2147/JMDH.S291757.

ЛИТЕРАТУРА

1. Габитова Н.Х., Казакова Ф.М., Хакимова Р.Н. Случай редкого заболевания у новорожденного ребенка. Практическая медицина. 2012; 9(65): 185–7.
2. Karnoub A.E., Weinberg R.A. Ras oncogenes: split personalities. Nature reviews. Molecular cell biology. 2008; 9(7): 517–31. DOI: 10.1038/nrm2438.
3. Dard L., Hubert C., Esteves P. et al. HRAS germline mutations impair LKB1/AMPK signaling and mitochondrial homeostasis in Costello syndrome models. The Journal of clinical investigation. 2022; 132(8): e131053. DOI: 10.1172/JCI131053.
4. Васина Т.Н., Зубцова Т.И., Ставцева С.Н. и др. Клиническая диагностика редкого наследственного заболевания — синдрома Костелло. Российский вестник перинатологии и педиатрии. 2010; 5: 27–30.
5. Vurallia D., Kosukcub C., Taskiranb E. et al. Hyperinsulinemic hypoglycemia in a patient with Costello syndrome: an etiology to consider in hypoglycemia. Molecular syndromology. 2020; 11: 207–16. DOI: 10.1159/000510171.
6. Aoki Y., Niihori T., Kawame H. et al. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nature genetics. 2005; 37: 1038–40. DOI: 10.1038/ng1641.
7. Харитонова Н.А., Басаргина М.А., Митиш М.Д. и др. Синдром Костелло в практике неонатолога. Клинический случай. Медицинский оппонент. 2021; 4(16): 76–80.
8. Costello J.M. A new syndrome: mental subnormality and nasal papillomata. Australian paedi-

atric journal. 1977; 13: 114–8. DOI: 10.1111/j.1440-1754.1977.tb01135.x.
9. Peixoto I.L., Carreno A.M., Prazeres V.M. et al. Syndrome in question. Costello syndrome. Anais brasileiros de dermatologia. 2014; 89(6): 1005–6. DOI: 10.1590/abd1806-4841.20143062.
10. Hinek A., Teitell M.A., Schoyer L. et al. Myocardial storage of chondroitin sulfate-containing moieties in Costello syndrome patients with severe hypertrophic cardiomyopathy. American journal of medical genetics. 2005; 133A(1): 1–12. DOI: 10.1002/ajmg.a.30495.
11. Privitera S., Prody C.A., Callahan J.W. et al. The 67-kDa enzymatically inactive alternatively spliced variant of beta-galactosidase is identical to the elastin/laminin-binding protein. The Journal of biological chemistry. 1998; 273(11): 6319–26. DOI: 10.1074/jbc.273.11.6319.
12. Gripp K.W., Morse L.A., Axelrad M. et al. Costello syndrome: Clinical phenotype, genotype, and management guidelines. American journal of medical genetics. 2019; 179(9): 1725–44. DOI: 10.1002/ajmg.a.61270.
13. Gripp K.W., Lin A.E., Nicholson L. et al. Further delineation of the phenotype resulting from BRAF or MEK1 germline mutations helps differentiate cardio-facio-cutaneous syndrome from Costello syndrome. American journal of medical genetics. 2007; 143A: 1472–80. DOI: 10.1002/ajmg.a.31815.
14. Gripp K.W., Hopkins E., Sol-Church K. et al. Phenotypic analysis of individuals with Costello syndrome due to HRAS p.G13C. American journal of medical genetics. 2011; 155A: 706–16. DOI: 10.1002/ajmg.a.33884.
15. McCormick E.M., Hopkins E., Conway L. et al. Assessing genotype-phenotype correlation in Costello syndrome using a severity score. Genetics in medicine: official journal of the American College of Medical Genetics. 2013; 15: 554–7. DOI: 10.1038/gim.2013.6.
16. Kerr B., Delrue M.-A., Sigaudy S. et al. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. Journal of medical genetics. 2006; 43: 401–5. DOI: 10.1136/jmg.2005.040352.
17. Martin R.A., Jones K.L. Delineation of the Costello syndrome. American journal of medical genetics. 1991; 41: 346–9. DOI: 10.1002/ajmg.1320410316.
18. Der Kaloustian V.M., Moroz B., McIntosh N. et al. Costello syndrome. American journal of medical genetics. 1991; 41: 69–73. DOI: 10.1002/ajmg.1320410118
19. Okamoto N., Chiyo H., Imai K. et al. A Japanese patient with the Costello syndrome. Human genetics. 1994; 93: 605–6. DOI: 10.1007/BF00202834.
20. Schwartz D.D., Katzenstein J.M., Highley E.J. et al. Age-related differences in prevalence of autism spectrum disorder symptoms in children and adolescents with Costello syndrome. American journal of medical genetics. 2017; Part A, 173(5): 1294–1300. DOI: 10.1002/ajmg.a.38174.
21. Young O., Perati S., Weiss L.A. et al. Age and ASD symptoms in Costello syndrome. American journal of medical genetics. 2018; Part A, 176(4): 1027–8. DOI: 10.1002/ajmg.a.38641.
22. Leoni C., Romeo D.M., Pelliccioni M. et al. Musculo-skeletal phenotype of Costello syndrome and cardio-facio-cutaneous syndrome: insights on the functional assessment status. Orphanet journal of rare diseases. 2021; 16(1): 43. DOI: 10.1186/s13023-021-01674-y.
23. Qian W., Zhang M., Huang H. et al. Costello syndrome with special cutaneous manifestations and HRAS G12D mutation: A case report and literature review. Molecular genetics & genomic medicine. 2021; 9(6): e1690. DOI: 10.1002/mgg3.1690.
24. Di Rocco M., Gatti R., Gandullia P. et al. Report on two patients with Costello syndrome and sialuria. American journal of medical genetics. 1993; 47(7): 1135–40. DOI: 10.1002/ajmg.1320470737.
25. Gripp K.W., Rauen K.A. Costello syndrome. Gene Reviews. 2020: 1–29.
26. Zampino G., Pantaleoni F., Carta C. et al. Diversity, parental germline origin, and phenotypic spectrum of de novo HRAS missense changes in Costello syndrome. Human mutation. 2007; 28(3): 265–72. DOI: 10.1002/humu.20431.
27. Umans S., Decock P., Fryns J.P. Costello syndrome: the natural history of a true postnatal growth retardation syndrome. Genetic counseling. 1995; 6(2): 121–5.
28. Fryns J.P., Vogels A., Haegeman J. et al. Costello syndrome: a postnatal growth retardation syndrome with distinct phenotype. Genetic counseling. 1994; 5(4): 337–43.
29. Costello J.M. Costello syndrome: update on the original cases and commentary. (Letter). American journal of medical genetics. 1996; 62(2): 199–201. DOI: 10.1002/ajmg.1320620203.
30. Kawame H., Matsui M., Kurosawa K. et al. Further delineation of the behavioral and neurologic features in Costello syndrome. American journal of medical genetics. 2003; 118A(1): 8–14. DOI: 10.1002/ajmg.a.10236.

31. Leoni C., Giorgio V., Onesimo R. et al. Impact of Costello syndrome on growth patterns. American journal of medical genetics. 2020; Part A, 182(11): 2797–9. DOI: 10.1002/ajmg.a.61812.
32. Ishida S., Mutsuga M., Fujita T. et al. Surgical techniques for infectious endocarditis of the mitral valve with hypertrophic cardiomyopathy in Costello syndrome. Journal of cardiology cases. 2022; 25(6): 367–9. DOI: 10.1016/j.jccase.2021.12.010.
33. Lin A.E., Rauen K.A., Gripp K.W. et al. Clarification of previously reported Costello syndrome patients. (Letter). American journal of medical genetics. 2008; Part A, 146A(7): 940–3. DOI: 10.1002/ajmg.a.32164.
34. Smith L.P., Podraza J., Proud V.K. Polyhydramnios, fetal overgrowth, and macrocephaly: prenatal ultrasound findings of Costello syndrome. American journal of medical genetics. 2009; Part A, 149A(4): 779–84. DOI: 10.1002/ajmg.a.32778.
35. Torrelo A., Lopez-Avila A., Mediero I.G. et al. Costello syndrome. Journal of the American Academy of Dermatology. 1995; 32(5 Pt 2): 904–7. DOI: 10.1016/0190-9622(95)91559-1.
36. Gripp K.W., Lin A.E. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from HRAS germline mutations. Genetics in medicine: official journal of the American College of Medical Genetics. 2012; 14(3): 285–92. DOI: 10.1038/gim.0b013e31822dd91f.
37. Leoni C., Flex E. Costello Syndrome: The Challenge of Hypoglycemia and Failure to Thrive. EBioMedicine. 2018; 27: 5–6. DOI: 10.1016/j.ebiom.2017.12.006.
38. Leoni C., Onesimo R., Giorgio V. et al. Understanding growth failure in Costello syndrome: increased resting energy expenditure. The Journal of pediatrics. 2016; 170: 322–4. DOI: 10.1016/j.jpeds.2015.11.076.
39. Sánchez-Montenegro C., Vilanova-Sánchez A., Barrena-Delfa S. et al. Costello Syndrome and Umbilical Ligament Rhabdomyosarcoma in Two Pediatric Patients: Case Reports and Review of the Literature. Case reports in genetics. 2017: 1587610. DOI: 10.1155/2017/1587610.
40. Feingold M. Costello syndrome and rhabdomyosarcoma. (Letter). Journal of medical genetics. 1999; 36(7): 582–3.
41. Kerr B., Eden O.B., Dandamudi R. et al. Costello syndrome: two cases with embryonal rhabdomyosarcoma. Journal of medical genetics. 1998; 35(12): 1036–9. DOI: 10.1136/jmg.35.12.1036.
42. Gripp K.W., Scott C.I., Nicholson L. et al. Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. American journal of medical genetics. 2002; 10(1): 80–7. DOI: 10.1002/ajmg.10241.
43. Menke J., Pauli S., Sigler M. et al. Uniparental trisomy of a mutated HRAS proto-oncogene in embryonal rhabdomyosarcoma of a patient with Costello syndrome. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(13): e62–5. DOI: 10.1200/JCO.2013.49.6539.
44. Moroni I., Bedeschi F., Luksch R. et al. Costello syndrome: a cancer predisposing syndrome? Clinical dysmorphology. 2000; 9(4), 265–8. DOI: 10.1097/00019605-200009040-00006.
45. Franceschini P., Licata D., Di Cara G. et al. Bladder carcinoma in Costello syndrome: report on a patient born to consanguineous parents and review. American journal of medical genetics. 1999; 86(2): 174–9.
46. Gripp K.W., Scott C.I., Nicholson L. et al. Second case of bladder carcinoma in a patient with Costello syndrome. (Letter). American journal of medical genetics. 2000; 90(3): 256–9. DOI: 10.1002/(sici)1096-8628(20000131)90:3<256::aid-ajmg16>3.0.co;2-d.
47. Lin A.E., O'Brien B., Demmer L.A. et al. Prenatal features of Costello syndrome: ultrasonographic fndings and atrial tachycardia. Prenatal diagnosis. 2009; 29(7): 682–90. DOI: 10.1002/pd.2276.
48. Leoni C., Viscogliosi G., Tartaglia M. et al. Multidisciplinary Management of Costello Syndrome: Current Perspectives. Journal of multidisciplinary healthcare. 2022; 15: 1277–96. DOI: 10.2147/JMDH.S291757.

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LISTERIOSIS. CONGENITAL NEONATAL SEPSIS. CLINICAL CASE

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Abstract. Neonatal listeriosis, related to intraurine infection, has a high mortality rate, this is due to the morphology and physiology of the pathogen, the rate of infection and the organs that are affected. This article discusses the main characteristics of the microorganism and the clinical case of the course of this disease.

Key worlds: *neonatal listeriosis; congenital neonatal sepsis; antibacterial therapy; ittraurine infections; hydrocephalus syndrome.*

ЛИСТЕРИОЗ. ВРОЖДЕННЫЙ НЕОНАТАЛЬНЫЙ СЕПСИС. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. Неонатальный листериоз, относящийся к внутриутробным инфекциям, имеет высокий процент летальности, связано это с морфологией и физиологией патогена, характером течения инфекции и органами, которые поражаются. В данной статье рассмотрены основные характеристики микроорганизма и клинический случай течения данного заболевания.

Ключевые слова: *неонатальный листериоз; врожденный неонатальный сепсис; антибактериальная терапия; внутриутробные инфекции; гидроцефальный синдром.*

Listeriosis is an infectious disease of bacterial etiology. The causative agent is *Lysteria monocytogenes*, a gram-positive facultative intracellular bacillus, stable in the environment and temperatures down to –1.5 °C. Outside the cell they are capable of "tumbling" motility; when moving inside the cell, the actin rockets mechanism is activated. It is a catalase-positive microorganism.

The disease is transmitted nutritionally (by eating unpasteurized milk, raw cheeses, meat, fish), the bacterium is able to pass through the intestinal barrier; invasion occurs due to the interaction

of internalin A (InlA) and E-cadherin (hEcad) with the participation of the phosphoinositide-3-kinase (PI3-K), which subsequently leads to secondary hematogenous dissemination [1, 2].

In addition to the nutritional route of transmission, a transplacental route is possible. When working with experimental models, it was proven that transplacental transmission occurs due to the interaction of the proteins internalin A (InlA) and B (InlB) on the bacterial cell surface in complex with c-Met and E-cadherin (hEcad), which being a transmembrane protein, is located on the apical and basement membranes of syncytiotrophoblasts (SYN) [3], and the interaction of InlB with c-Met is critical for the activation of PI3-K in SYN and is required for InlA-mediated entry of *L. monocytogenes* across the placental barrier [4]. The possibility of its participation in this type of distribution of internalin P (InlP) is also currently being studied [14].

The toxin synthesized by bacteria, listeriolysin O (LLO), which is necessary for the exit of the bacterial cell from the host cell vacuole, has an active influence on the infection process; its ability to modulate signaling pathways is also considered in modern studies [5]. Phosphatidylinositol-specific lipase C (PICA) and lecithinase are also required for phagosome exit, and metalloproteinase carries out post-translational modification of lecithinase.

The ActA protein regulates actin polymerization, mediating bacterial movement and invasion [7].

Risk factors are pregnancy, immunodeficiency, and old age. The incubation period ranges from 3 to 70 days, with an average of 21 days [8, 9].

The most common form of listeriosis is neurolisteriosis in pregnant women, which is extremely rare. In newborns, two forms of listeriosis are distinguished: with early onset with the manifestation of infection on the 1st–2nd day after birth, the mortality rate can reach 50%; late-onset listeriosis develops after 10–12 days and is associated with nosocomial infection [15, 16].

Infection in the first half of pregnancy is accompanied by chorioamnionitis, flu-like symptoms, with fever observed in 85% of cases, spontaneous abortions, and the formation of fetal malformations [10, 11].

Infection in the second half of pregnancy leads to premature labor, stillbirth, meningitis, sepsis, neonatal pneumonia, and damage to the nervous system [12, 13].

Infection as a result of aspiration of amniotic fluid intrapartum is also possible. Such infection is characterized by a later development of symptoms, usually in the form of meningitis. With such an infection, transient colonization is possible, which will not lead to the development of the disease.

A damage to the fetus is associated both directly with an infection and decrease in the number or disturbances in the functioning of T-regulatory cells (Treg), which consists in a decrease in their regulatory ability, which leads to immune-mediated fetal death [17].The stimulation of immune system cells by cytokines produced by T-lymphocytes leads to the formation of granulomas — listeriomas, which are systemic in nature and are considered as granulomatous sepsis.

CLINICAL CASE

G.K. was born prematurely at 25 6/7 weeks, as a result of the second pregnancy, the first was in 2019, term labor. The course of pregnancy was unremarkable; according to ultrasound at the 25th week, polyhydramnios, grade III hemodynamic disturbances, and chronic placental insufficiency were revealed. The birth weight was 940 g (1 centile corridor), the body length was 30 cm (1 centile corridor), the head circumference was 25 cm (1 centile corridor), the chest circumference was 23 cm (1 centile corridor). Apgar score was 2/3 points.

The condition at birth is regarded as extremely severe due to respiratory failure, prematurity, morphofunctional immaturity, and severe intrapartum asphyxia. Resuscitation measures were carried out and she was connected to an artificial lung ventilation device (ALV). She responded to the examination with increased motor activity, muscle tone and reflexes of the newborns were reduced. Respiration was weakened, crepitus was heard, saturation decreased to 70%, weakened breathing on the right — right-sided hydrothorax, according to ultrasound of the pleural cavities on both sides, traces of effusion were determined, the lungs showed signs of interstitial inflammation. A pleural puncture and drainage were performed.

A clinical blood test revealed thrombocytopenia and anemia. Acid-base state (ABS) — mixed acidosis, lactic acidosis. EchoCG — tricuspid regurgitation of the 1st degree. Neurosonography (NSG) — increased periventricular echo density in the frontal-parietal-occipital regions. Full-blooded

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choroid plexuses, intraventricular hemorrhages of degree II on the left, degree I on the right, expansion of the occipital horns.

According to ultrasound of the abdominal organs and kidneys, a diffuse change in the renal parenchyma was observed with depletion of blood flow in the periphery, a moderate amount of free fluid in all parts of the abdominal cavity of an anechoic nature.

Examination by an ophthalmologist — the retina is in the stage of vascularization (zone II).

According to the results of histology of the placenta, the following were identified: acute focal chorioamnionitis, choriodeciduitis, acute subchorionitis, productive placentitis, chronic subcompensated placental insufficiency, acute placental insufficiency.

Based on the totality of clinical and laboratory data, a diagnosis of "early neonatal sepsis" was made.

According to blood and sputum cultures and from the ear fold, there was growth of bacteria of the genus *Lysteria*, as a result of which the child was diagnosed with neonatal listeriosis. An antibacterial therapy was prescribed with ciprofloxacin, amikacin and meropenem.

In the first two weeks, the condition was interpreted as extremely severe, a negative intracranial clinical picture was observed with an increase in intracranial hemorrhages, central hemodynamic parameters were unstable, inotropic and vasopressor therapy was carried out. Due to insufficient diuresis, edema syndrome developed to anasarca; a laparocentesis was performed due to ascites. In the second week, the drainage in the abdominal cavity began to drain intestinal contents; during the operation, it was discovered that the wall of the ileum in the distal section for 15 cm was flabby, with multiple perforations, and therefore a section of the small intestine was resected ileocecal angle, a double enterocolostomy was performed, by the end of the second week the child's condition worsened due to the cessation of the stoma and a change in the infection status with an increase in leukocytosis. A lumbar puncture was performed due to hydrocephalic syndrome.

According to neurosonography, a picture of slow negative dynamics of increase in ventriculomegaly was observed against the background of persistent increased periventricular echo density in the frontal-parietal-occipital regions, full-blooded choroid plexuses, intraventricular hemorrhages of the second degree on the left, second degree on the right, and a pronounced expansion of the occipital horns. The hydrocephalic syndrome did not progress after lumbar puncture. According to the results of a repeat study, two days later there was a stabilization of ventriculomegaly.

During the third and fourth weeks, the child's condition was extremely severe with positive dynamics, the course of the disease was wavy, the exit of the eventrated strand of the omentum between the sutures at the diverting stoma was noted, surgical intervention was performed, in addition, due to anemia and hypocoagulation, a transfusion of erythrocyte suspension and fresh frozen plasma was carried out. The dynamics showed stabilization of the condition; due to the possibility of spontaneous breathing, the child was extubated, but respiratory support through nasal cannulas was maintained.

By the end of the fourth week, the condition worsened against the background of progression of the neurological clinical picture with manifestations in the form of apnea.

Subsequently, the condition stabilized, positive dynamics were observed during the treatment, there were no signs of increasing respiratory failure, the patient needed respiratory support through nasal cannulas. Central hemodynamic parameters were compensated.

According to echocardiography, left ventricular hypertrophy was observed, minimal without dynamic obstruction of the left ventricular outflow tract (LVOT). A tricuspid regurgitation of the I degree was noted.

The child was transferred to the neonatal pathology department, where he remained until the operation to close the enterocolostomy; four days later, a repeat operation was performed due to anastomotic failure; relaparatomy, resection of the anastomotic area, and enterocolostomy were performed. Taking into account the data of cultures of the contents of the abdominal cavity with seeding of *K. pneumonia* and *S. maltophilia*, as well as the failure of the anastomosis, which could be caused by the course of the infectious process, a change in antibacterial therapy was carried out according to sensitivity, ciprofloxacin was prescribed, and amikacin, meropenem were canceled.

Two weeks after the operation, the condition worsened: pronounced retraction of the upper aperture of the chest and intercostal spaces during inspiration, pronounced stridor, an attempt

was made to relieve swelling of the larynx and upper respiratory tract by inhalation with adrenaline and dexazone. Intubation was performed due to persistent decompensated respiratory acidosis according to ABS data and severe disturbances in respiratory mechanics such as inspiratory dyspnea. A moderate amount of white sputum was sanitized from the tracheobronchial tree; according to its culture, a fungal infection was detected, and therapy with amphotericin B was started. After stabilization of the condition, a T-shaped ileocoloanastomosis was performed.

The repeated neurosonography was without changes, dynamic ultrasonographic (US) monitoring revealed an increase in the dorsal horns and the cisterna magna, a retrocerebellar cyst/ cerebellar hypoplasia was suspecte. An magnetic resonance imaging of the brain was performed there were signs of cortical-subcortical subatrophy of the cerebral hemispheres and cerebellum, normotonic occlusion at the level of the midbrain aqueduct, triventricular hydrocephalus due to subarachnoid hemorrhage and bilateral intraventricular hemorrhage due to prematurity.

According to US monitoring, the hydrocephalic syndrome did not progress. The Observation was continued by a neurologist together with surgeons due to the need for surgery to close the colostomy. According to US monitoring, it was established that the hydrocephalic syndrome does not progress, there is a developmental delay, and torticollis.

In the postoperative period, the condition was assessed as severe; subsegmental atelectasis was detected in the right lung, for which X-ray control was carried out. Considering the positive X-ray picture and the absence of respiratory failure, no further therapy was needed. A Dynamic observation by an ophthalmologist for retinopathy of prematurity was continued, stabilization was noted.

At the moment, the child's condition has been stabilized due to previous treatment; the girl is under constant observation by pediatricians, neurologists and ophthalmologists.

There is a severe delay in psychomotor development, organic damage to the central nervous system (CNS) as a consequence of hemorrhage in the germinal matrix of both hemispheres of the cerebrum, the vermis and the right hemisphere of the cerebellum, in the lateral and fourth ventricles, the pontocerebellar cistern, right-sided chronic subdural hematoma, stenosis of the aqueduct, expansion of the lateral and third ventricle of the brain, atrophy of the corpus callosum, decrease in the volume of white matter of the brain, atrophy of the vermis, cerebellar hemispheres, pons, medulla oblongata. The Hydrocephalic syndrome is compensated. A Movement disorders syndrome, pyramidal insufficiency, and muscular dystonia syndrome are noted.

CONCLUSION

The described clinical case demonstrates the severity of congenital listeriosis, with the neurological clinical picture manifested by multiple brain injuries. In addition to the central nervous system, other organs and systems are also negatively affected. Stabilization of the condition was achieved through antibacterial, vasopressor and symptomatic therapy, as well as through timely surgical treatment of manifestations of sepsis.

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 there have no competing interests.

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

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

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REFERENCES / ЛИТЕРАТУРА

1. Ireton K., Payrastre B., Chap H. et al. A role for phosphoinositide 3-kinase in bacterial invasion. Science. 1996; 274(5288): 780–2.
2. Ireton K., Payrastre B., Cossart P. The listeria monocytogenes protein InlB is an agonist of mammalian phosphoinositide 3-kinase. J Biol Chem. 1999; 274: 24.
3. Lecuit M., Nelson D.M., Smith S.D. et al. Targeting and crossing of the human maternofetal barrier by Listeria monocytogenes: role of internalin interaction with trophoblast E-cadherin. Proc Natl Acad Sci USA. 2004; 101: 6152–7.
4. Gessain G., Tsai Y.H., Travier L. et al. PI3-kinase activation is critical for host barrier permissiveness to Listeria monocytogenes. J Exp Med. 2015; 212(2): 165–83.
5. Hamon M.A., Ribet D., Stavru F. et al. Listeriolysin O: the Swiss army knife of Listeria. Trends Microbiol. 2012; 20(8): 360–8.
6. Le Monnier A., Autret N., Join-Lambert O.F. et al. ActA is required for crossing of the fetoplacental barrier by Listeria monocytogenes. Infect Immun. 2007; 75(2): 950–7.
7. Angelo K.M., Jackson K.A., Wong K.K. et al. Assessment of the Incubation Period for Invasive Listeriosis. Clin Infect Dis. 2016; 63: 1487–9.
8. Goulet V., King L.A., Vaillant V. et al. What is the incubation period for listeriosis? BMC Infect Dis. 2013; 13: 11.
9. Lamont R.F., Sobel J., Mazaki-Tovi S. et al. Listeriosis in human pregnancy: a systematic review. J Perinat Med. 2011; 39: 227–36. DOI: 10.1515/JPM.2011.035.
10. Mylonakis E., Paliou M., Hohmann E.L. et al. Listeriosis during pregnancy: a case series and review of 222 cases. Medicine (Baltimore). 2002; 81: 260–9. DOI: 10.1097/00005792-200207000-00002.
11. Robbins J.R., Bakardjiev A.I. Pathogens and the placental fortress. Curr Opin Microbiol. 2012; 15: 36–43. DOI: 10.1016/j.mib.2011.11.006.
12. Vigliani M.B., Bakardjiev A.I. First trimester typhoid fever with vertical transmission of Salmonella Typhi, an intracellular organism. Case Rep Med. 2013; 2013: 973297. DOI: 10.1155/2013/973297.
13. Faralla C., Bastounis E.E., Ortega F.E. et al. Listeria monocytogenes InlP interacts with afadin and facilitates basement membrane crossing. PLoS Pathog. 2018; 14(5): e1007094.
14. Angelo K.M., Jackson K.A. Wong K.K. et al. Assessment of the Incubation Period for Invasive Listeriosis. Clin Infect Dis. 2016; 63: 1487–9.
15. Goulet V., King L.A., Vaillant V. et al. What is the incubation period for listeriosis? BMC Infect Dis. 2013; 13: 11.
16. Rowe J.H., Ertelt J.M., Xin L. et al. Listeria monocytogenes cytoplasmic entry induces fetal wastage by disrupting maternal Foxp3+ regulatory T-cell-sustained fetal tolerance. PLoS Pathog. 2012; 8(8): e1002873.

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RHABDOMYOLYSIS AS A CONSEQUENCE OF EXCESSIVE PHYSICAL ACTIVITY IN CHILDREN AND ADOLESCENTS

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Abstract. Rhabdomyolysis remains a major diagnostic and therapeutic and preventive problem for clinicians, especially when working with athletes of child and adolescent age. A diverse etiology, the absence of specific symptoms, late diagnosis, the development of systemic complications worsen the prognosis of the disease and complicate treatment. Rhabdomyolysis associated with physical activity in children and adolescents is non-traumatic in origin, is often caused by hereditary causes and is provoked against the background of infectious diseases and metabolic disorders. Timely implementation of correct infusion therapy remains the cornerstone of the treatment of rhabdomyolysis. A clinical case of successful treatment of a teenager with rhabdomyolysis complicated by acute kidney injury is presented.

Key words: *non-traumatic rhabdomyolysis; children and adolescents; acute kidney injury; literature review; clinical case.*

РАБДОМИОЛИЗ КАК СЛЕДСТВИЕ ЧРЕЗМЕРНОЙ ФИЗИЧЕСКОЙ НАГРУЗКИ У ДЕТЕЙ И ПОДРОСТКОВ

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Резюме. Рабдомиолиз остается большой диагностической и лечебно-профилактической проблемой для клиницистов, особенно при работе со спортсменами детского и подросткового возраста. Разнообразная этиология, отсутствие специфических симптомов, поздняя диагностика, развитие системных осложнений ухудшают прогноз заболевания и затрудняют лечение. Рабдомиолиз, связанный с физической нагрузкой, у детей и подростков по своему происхождению относится к нетравматическому, часто обусловлен наслед-

ственными причинами и провоцируется на фоне инфекционных заболеваний и нарушений метаболизма. Своевременное проведение корректной инфузионной терапии остается краеугольным камнем лечения рабдомиолиза. Представлен клинический случай успешного лечения подростка с рабдомиолизом, осложненным острым поражение почек.

Ключевые слова: *нетравматический рабдомиолиз; дети и подростки; острое повреждение почек; обзор литературы; клинический случай.*

INTRODUCTION

Rhabdomyolysis (ICD-10 code: M60–M63 Muscle diseases) is a clinical and laboratory syndrome of damage and destruction of myocytes of striated muscles, manifested by myalgia, muscle weakness, swelling of the affected muscles, a decrease in volume and the appearance of dark brown urine due to the release and entry into the systemic circulation of myolysis products, primarily myoglobin (MG), as well as creatine phosphokinase (CPK), lysosomal and mitochondrial enzymes, histamine, serotonin, oligo- and polypeptides and others, with the subsequent manifestation of endogenous intoxication. There are traumatic and non-traumatic rhabdomyolysis [1, 2]. In general medical practice, rhabdomyolysis is more often associated with traumatic damage to muscle tissue [3]. The lack of alertness of pediatricians regarding the possibility of developing non-traumatic rhabdomyolysis in children and adolescents can lead to diagnostic errors and an increase in adverse outcomes [4]. Among the many causes of non-traumatic rhabdomyolysis, one should remember the reality of the threat of muscle tissue damage due to high-intensity physical activity [5, 6].

In severe cases, rhabdomyolysis is an extreme degree of myopathy with the subsequent development of acute kidney injury (AKI), severe disturbances of homeostasis, disseminated intravascular coagulation syndrome, multiple organ failure with a threat to the patient's life [7, 8]. An Acute pigmented nephropathy, or myoglobinuria-induced AKI, myoglobinuric nephrosis, myorenal syndrome arethe most common systemic complications of rhabdomyolysis.

The occurrence of non-traumatic rhabdomyolysis in adult and pediatric population has not been precisely established, but the frequency of AKI in this pathology is known and, according to various sources, ranges from 10 to 55%, which indicates the relevance of studying this problem [9]. Among the causes of AKI, the share of rhabdomyolysis reaches 25%, and the mortality rate in patients with rhabdomyolysis complicated by AKI exceeds 10% [3, 10].

ETIOLOGY OF RHABDOMYOLYSIS

The incidence of non-traumatic rhabdomyolysis depends on the etiology (sporadic and recurrent forms) [4, 11, 12]. In childhood, adolescence and young adulthood, the development of non-traumatic rhabdomyolysis is facilitated by hereditary metabolic disorders, and the disease is characterized by a relapsing course [13–15]. An autosomal recessively inherited disease from the group of genetic disorders of fatty acids transport, namely the myopathic form of carnitine palmitoyltransferase II deficiency (CPT II), is one of the common causes of myoglobinuria [16, 17]. Other hereditary causes of rhabdomyolysis may include very long chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy, and idiopathic paroxysmal rhabdomyolysis (Meyer–Betz syndrome) [12, 14, 18].

Triggers of non-traumatic rhabdomyolysis in childhood and adolescence, in addition to prolonged heavy physical activity, are infectious diseases of viral (influenza, COVID-19, enteroviruses and other agents) [19–21] and bacterial etiology (rickettsiosis, legionellosis, salmonellosis, tularemia, malaria, etc) [22], convulsions, hypothermia, overheating, stressful situations, metabolic disorders (water intoxication, dehydration, hypokalemia, hypo- and hypercalcemia, fasting) [23, 24], some drugs [4, 5, 25, 26], as well as idiopathic inflammatory myopathies (dermatomyositis, polymyositis or antisynthetase syndrome) [27].

PATHOGENESIS OF RHABDOMYOLYSIS

In *traumatic rhabdomyolysis* destruction of skeletal muscles occurs as a result of direct impact on them, damage or compression (compression syndrome), ischemia of the limbs due to disturbances in the main blood flow and increased tissue pressure inside the fascial spaces. The Disruption of arterial blood flow lasting more than 4 hours leads to muscle changes, the entry of myolysis products into the systemic circulation and the occurrence of multiple organ disorders. A type of long-term compression syndrome is positional ischemia syndrome, in which muscle compression is carried out

by the weight of one's own body while the patient is unconscious [28]. A Long-term immobilization of a limb with a plaster cast can also cause an increase in MG levels and CPK activity in the blood serum [29]. It should be noted that some authors incorrectly classify rhabdomyolysis due to excessive physical activity as traumatic [30].

The pathophysiological mechanisms of the development of non-traumatic rhabdomyolysis are different and in most cases are assumed [29]. Rhabdomyolysis during very strenuous exercise is caused by insufficient oxygenation of the skeletal muscles, as well as dehydration due to excessive sweating.

As a result of muscle breakdown, ATP synthesis switches from the aerobic to anaerobic pathway, in which ATP reserves are quickly depleted; a subsequent accumulation of lactic acid leads to intracellular acidosis. Due to hypoxia and a decrease in pH, the functioning of K^+-Na^+-ATPase is disrupted, while K^+ ions leave the cells into the vascular bed, and Ca^{2+} and Na^+ ions move in the opposite direction, which contributes to an increase in osmotic pressure in the myocyte, edema and disruption of its integrity, increased lipid peroxidation in cell membranes with the formation of peroxyl radicals. The peroxyl radicals, during interaction with the structural units of cell membranes, cause fragmentation of proteins, damage to DNA and lipids, which inhibits bioenergetic processes in myocytes, leading to their death, this is accompanied by an increase in the content of CPK and MG in the blood. The MG as an oxygen transporter ensures oxygenation of muscles during their contraction. A hypermyoglobinemia is a consequence of muscle damage and a marker of endotoxemia, since there is a direct relationship between serum MG levels and the severity of tissue hypoxia. An oxidative stress is a leading factor in the development of AKI in rhabdomyolysis [31]. The CPK is a component of muscle cells and one of the key enzymes of energy metabolism. The level of CPK, as a rule, correlates with the content of MG, but its peak content is reached much later. The MG is able to penetrate the glomerular basement membrane, bind to the Tamm–Horsfall protein and cause tubular obstruction, forming a sediment in the lumen of the distal tubules in the form of pigmented cylinders. Against the background of existing hypovolemia, the MG causes renal vasoconstriction and additional activation of the renin-angiotensin-aldosterone system. The pathogenesis of AKI due to rhabdomyolysis includes a hypovolemia, decreased renal perfusion, obstruction of the renal tubules by myoglobin casts, and myoglobinuric nephrosis [32]. At the same time, if rhabdomyolysis is immediately identified and adequately treated with ample hydration, the condition of most patients soon improves and no complications are observed [6].

CLINICAL PICTURE OF RHABDOMYOLYSIS

Clinical manifestations of exercise-related rhabdomyolysis are characterized by a triad of symptoms: muscle pain, weakness, change in urine color (reddish-brown, brown). Proximal muscle groups (shoulders, hips, lower back, calves) are most often affected. In severe cases nausea, vomiting, disturbances of consciousness of varying severity and decreased diuresis up to anuria are observed [5, 33]. The subclinical form of rhabdomyolysis is characterized by "tenderness" of certain muscle groups and mild pain during movement, felt 1-2 days after exercise, which is called delayed onset muscle soreness syndrome. Sometimes patients do not present any complaints; in these cases the disease is diagnosed by changes in biochemical blood parameters [34].

LABORATORY METHODS FOR DIAGNOSTICS OF RHABDOMYOLYSIS

Biochemical blood test. The rhabdomyolysis (myoglobinuria) is diagnosed when the serum myoglobin level exceeds 80 ng/ml and the creatine kinase level increases 5 times the upper limit of normal, exceeding 1000 U/L [6, 7]. The concentration of MG reaches a maximum on the 1st day of the disease, CPK — on the 3rd–5th day, which is explained by the low rate of elimination of CPK from the bloodstream. The increase in MG in the blood outpaces the increase in the activity of the enzymes lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). CPK indicators are different depend on the gender, age, race, and level of physical development of patients. The level of CPK increases during periods of intensive growth in children [35]. Characteristic changes for this pathology are acidosis, increased creatinine, uric acid, C-reactive protein, hyperkalemia, hyperphosphatemia, hypocalcemia [5].

Assessment of diuresis. A decrease in urine output by 8–10% indicates the onset of AKI development. With further development of the pathological process, the diuresis decreases by 25% or more; an anuria may develop. During the recovery period, the daily diuresis increases significantly.

Urine analysis. The most typical changes in urine color from dark brown to black, impaired urine density, proteinuria, acetonuria, and the presence of pigmented casts [5, 16, 27]. The hematuria may occur [6].

Genetic research. Molecular genetic studies are usually carried out (next generation sequencing (NGS), fluorescence *in situ* hybridization (FISH test), polymerase chain reaction (PCR), Sanger sequencing, etc.) to detect hereditary causes of rhabdomyolysis, these studies are aimed at identification of gene polymorphisms affecting the activity of enzymes regulating lipid metabolism [5, 13, 15].

With the advent of tandem mass spectrometry (TMS), early diagnosis of a large number of hereditary metabolic diseases, the age of manifestation and the range of clinical manifestations of which is very variable, has become possible [36]. Certain variants of defects in mitochondrial β-oxidation of fatty acids determine the development of non-traumatic rhabdomyolysis. Thus, myopathy, manifested by exercise intolerance, is caused by a deficiency of carnitine palmitoyltransferase type 2 (CPT 2). This disease typically begins in adolescence or adulthood. Episodes of rhabdomyolysis may occur with an associated risk of developing AKI. The TMS method detects an increase in long-chain acylcarnitines (C16, C18), and determines a mutation in the *CPT2* gene, which is mapped to 1p32.3.

The another inherited cause of rhabdomyolysis may be very long-chain fatty acid acyl-CoA dehydrogenase (VLCAD) deficiency. Complete deficiency manifests itself in the neonatal period with severe cardiomyopathy and is often fatal. A partial failure begins in adolescence or adulthood with hypoketotic hypoglycemia, myopathy, and rhabdomyolysis. The *ACADVL* gene is located on 17p13.1 [37]. During TMS, an increase in acylcarnitine (C14) in the blood is detected.

Mitochondrial trifunctional protein (TFP) deficiency and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency have similar clinical manifestations, but TFP is more severe. Patients have cardiomyopathy, hypoketotic hypoglycemia, liver dysfunction (Reye's syndrome), cholestasis, and rhabdomyolysis. The half of patients have pigmentary retinopathy. In LCHAD a mutation in the *HADHA* gene (2p23.3) is detected [37], in TFP — *HADHA* (2p23.3), *HADHB* (2p23.3). When performing TMS, patients with TFP show an increase in C16OH acylcarnitine, and in patients with LCHAD, an increase in C16OH and C18OH acylcarnitines [37]. To accurately verify the diagnosis after TMS, a molecular genetic study is performed to detect pathogenic nucleotide variants, structural rearrangements and variations in the copy number of relevant genes [36].

INSTRUMENTAL METHODS FOR DIAGNOSTICS OF RHABDOMYOLYSIS

Ultrasound. In the early stages of skeletal muscle necrosis, ultrasound signs of edema and destruction of muscle tissue are detected: a diffuse increase or decrease in the echogenicity of the muscles and their thickening are determined. There is a decrease in structure and erasure of the muscle pattern, arch-like bulges of the muscle fascia, and the appearance of intermuscular fluid inclusions are detected. The formation of calcifications indicates a late stage of the disease. However, changes detected in the gray scale mode are not specific to rhabdomyolysis and can be observed in other pathological muscle conditions. A Skeletal muscle ultrasound is more often used when the patient's condition is severe and magnetic resonance imaging is unavailable [38].

Compression sonoelastography and shear wave sonoelastography. These methods are used for a more accurate assessment of structural changes in muscles, since they allow the assessment of not only qualitative, but also quantitative indicators of muscle density [32, 39].

Magnetic resonance imaging (MRI). The MRI is a highly informative and sensitive method for diagnosing rhabdomyolysis, especially in cases of atypical distribution of damage, involvement of small muscle groups and a high probability of compressive effects on the neurovascular bundles. According to the MRI, muscles affected by rhabdomyolysis have increased signal intensity in T2-weighted and STIR modes, as well as reduced intensity in T1-weighted modes. The T2-weighted examination allows to identify areas of muscle necrosis. An improved muscle MRI technique with quantitative assessment of T2 relaxation time has high sensitivity and specificity (94 and 82%, respectively) in the diagnosis of rhabdomyolysis [40, 41].

Morphological diagnosis of skeletal muscle necrosis. In some cases, if rhabdomyolysis is suspected, a biopsy and histomorphological examination of the muscle tissue involved in the pathological process are performed [41].

In forensic medical expert practice, there are cases when differential diagnosis of rhabdomyolysis of a traumatic and non-traumatic nature is

necessary, which is achieved based on the results of a histological examination of autopsy material of skeletal muscles [28].

DIFFERENTIAL DIAGNOSTICS

The clinical picture of non-traumatic rhabdomyolysis is quite nonspecific, and requires additional research, including the exclusion of glomerulonephritis and a number of infectious diseases (viral hepatitis, leptospirosis, etc.).

TREATMENT OF RHABDOMYOLYSIS

Patients with rhabdomyolysis need the earliest possible appointment of adequate rehydration infusion therapy, prescribed in the first 6 hours from the moment of muscle damage, correction of electrolyte disturbances (hypo- and hyperkalemia, hyperphosphatemia). A diet limited in protein and potassium-containing foods is prescribed. The volume of drug therapy depends on the severity of the patient's condition and is aimed at preventing the development of AKI. Extracorporeal detoxification methods, eliminating myolysis products from the systemic circulation, are the most effective methods for treating complications of rhabdomyolysis [1, 4, 8, 32].

PROGNOSIS

The prognosis of rhabdomyolysis is determined by the risk of developing life-threatening conditions. The AKI, hyperkalemia accompanied by severe arrhythmias, hypovolemic shock and disseminated intravascular coagulation syndrome can be the causes of death in patients.

Severe rhabdomyolysis is accompanied by the development of a secondary immunodeficiency state, which promotes the activation of an opportunistic microbiome with a high risk of developing the manifestation of sepsis [8, 19, 28].

To illustrate the above, we present one of the clinical cases of typical non-traumatic rhabdomyolysis in a teenager, caused by intense physical activity and complicated by impaired renal function in the acute period of the disease.

CLINICAL CASE

Patient M., 14 years old, was urgently admitted by ambulance to the emergency department of St. Petersburg State Budgetary Institution Children's City Hospital № 2 of St. Mary Magdalene, accompanied by his mother, with a diagnosis of closed injury of the lumbar spine dated 08.11. Macrohematuria? Myositis of the back and thighs.

At the time of admission to the hospital, there were complaints of severe back pain, change in the color of urine (the color of "dark beer").

Anamnesis morbi. On November 7th, during classes in the volleyball section, the patient performed the same type of exercises on the hyperextension trainer for a long time. He limited his water load during classes. By the evening a pain appeared in the back and calf muscles, the muscles of the back of the thigh. Over the next two days the pain increased without any effect on oral Nurofen. On November 9th severe weakness appeared, the urine darkened to the color of "dark beer". The body temperature increased to 37.3 °C.

Anamnesis vitae. He grew and developed without signs of lag. The vaccination history corresponds to the vaccination calendar by age. He is not registered at the dispensary for diseases. There is no allergic history. There were no injuries or operations. A heredity is not burdened. An Epidemiological history is unremarkable. Periodically over the last year, a myalgia has been observed after prolonged physical exertion, which resolves within two days.

Objective examination data upon admission to the hospital. The general condition is moderate. A consciousness is clear. The food is satisfactory. Height — 182 cm (7 points; high physical development). Weight — 65 kg (4 points; harmonious development). BMI — 19.7 (within normal values). Heart rate — 66 per minute. Blood pressure — 120/80–110/70 mm Hg. The body temperature is 37.0 °C. A consciousness is clear. The physique is correct. The skin is pink, without rash. Visible mucous membranes are pink. The tongue is clean and moist. The boundaries of relative cardiac dullness are not expanded. Heart sounds are clear and rhythmic. The percussion sound above the lungs is clear. The breathing is vesicular, carried out in all fields, without wheezes. The abdomen is symmetrical, participates in the act of breathing, is accessible to deep palpation, is not swollen, soft, painless, pathological formations are not palpable. Symptoms of peritoneal irritation are negative. The liver is not enlarged. The spleen is not palpable. The chair is decorated. The urination is not difficult. A urine is the color of «dark-beer».

Local status. A percussion of the spinous processes of the spine is painless. The back muscles are swollen paravertebrally, their palpation is sharply painful; the muscles of the back of the thighs are painful on palpation.

Data from laboratory research methods. Blood test: 10.11 — hemoglobin — 142 g/l; erythro-

cytes — 4.84×10^{12}/l; hematocrit — 0.39; average hemoglobin concentration — 366 g/l; average hemoglobin content — 29.9 pg; platelets — 238.1×10^{9}/l; leukocytes — 7.7×10^{9}/l (11.14 — 5.3×10^{9}/l; 24.11 — 5.0×10^{9}/l); neutrophils — 70.7%; neutrophils abs. quantity — 5.47×10^{9}/l (24.11 — 2.29×10^{9}/l); eosinophils — 3.8%; basophils — 0.38%; lymphocytes 19% (11.11 — 27.1%); lymphocytes abs. quantity — 1.47×109/l; monocytes — 10% (24.11 — 9.1%); ESR — 5 mm/h. Changes in the blood test on 10.11 indicated the presence of indirect signs of hypoxia (increased average hemoglobin concentration; norm 346–354 g/l) [42] and inflammatory manifestations in the form of neutrophilia (relative and absolute), lymphocytopenia (relative and absolute), monocytosis. In the dynamics of observation (11.11, 14.11, 24.11) the appearance of leukopenia, neutropenia, and persistence of monocytosis was noted, which, along with low-grade fever, did not exclude the course of an infectious disease.

Biochemical blood test: 10.11 — increased ALT — 267 units/l (24.11 — 39 units/l); AST — 1218 units/l (11.11 — 1316 units/l; 24.11 — 23 units/l); LDH — 2156 units/l (24.11 — 436 units/l); CPK — 107,990 units/l (24.11 — 238 units/l); CPK-MB — 3762 units/l; myoglobin — 1801.1 μg/l; total bilirubin — 31.3 μmol/l; direct bilirubin — 12.1 μmol/l; glucose — 5.8 mmol/l (24.11 — 4.9 mmol/l); low-density lipoprotein cholesterol — 1.9 mmol/l; phosphorus — 1.48 mmol/l; chlorine — 109 mmol/l (24.11 — 105 mmol/l) with normal troponin levels — 0.02 ng/ml; C-reactive protein — 2 mg/l; creatinine — 86 mmol/l; urea — 3.9 mmol/l; rheumatoid factor — 3 IU/ml; gamma-glutamate transferase — 18.2 units/l; total protein — 66 g/l; albumin — 44 g/l; total cholesterol — 3.5 mmol/l; high-density lipoprotein cholesterol — 1.21 mmol/l; uric acid — 293 mmol/l; total calcium — 2.45 mmol/l; potassium — 4.1 mmol/l; sodium — 146 mmol/l; iron — 24.6 μmol/ml. A glomerular filtration rate (GFR) according to the Schwartz formula at admission was 83 ml/min/1.73 m^2, at discharge — 130.4 ml/min/1.73 m^2. The values and dynamics of AST, ALT, LDH, CPK, CPK-MB, myoglobin, electrolytes (phosphorus, chlorine), GFR indicated rhabdomyolysis with AKI without a decrease in nitrogen excretory function, toxic hepatitis and the presence of cholestasis. A dyslipidemia reflected the patient's underlying lipid metabolism disorder.

A study of humoral immunity factors in the blood revealed a decrease in IgG (10.11 — 621 mg/dl; 24.11 — 663 mg/dl) with normal levels of IgA and IgM — 117 and 76 mg/dl, respectively, complement components C3 — 117 mg/dl and C4 — 29 mg/dl.

Urine examination: 09.11 — quantity — 40 ml (24.11 — 80 ml); color brown (24.11 — straw yellow); transparency — slightly turbid; relative density — 1.030 (24.11 — 1.018); the reaction is slightly acidic; protein — 0 g/l; glucose — 0 g/l; hemoglobin 10.11 — 3+. A microscopy of urine sediment: 09.11 — squamous epithelium — 0–1 in the field of view (n/z); leukocytes — 3–5 in p/zr; unchanged erythrocytes — 1–2 in p/zr (10.11 — 15–20 in p/zr); changed erythrocytes — 1–3 in p/zr; mucus — 2–3; oxalate salts — 1–2; urate salts — 0–1. A daily diuresis 11.11 — 950 ml; daily protein — 0.170 g. An urine culture is sterile. A study of urine test data revealed signs characteristic of rhabdomyolysis: discoloration, hematuria, proteinuria [6].

Coagulogram parameters are within normal limits. A blood test for RNGA with salmonellosis, pseudotuberculosis, dysentery (Sonne, Flexner, Newcastle), yersinia (O3 and O9) diagnosticums is negative. Nasopharyngeal swab — rapid antigen test for COVID-19 — negative. A serum antistreptolysin-O was slightly elevated — 211 IU/ml. The study of antibodies to helminthiasis (ascariasis, toxocariasis, anisakiasis) in the blood is negative. The study of IgG and IgM to cytomegalovirus, IgG to herpes virus type 6, IgM to capsid, nuclear and early antigens of the Epstein-Barr virus — negative, IgG to herpes viruses types 1 and 2 — titer 1:1600 (positive) with normal IgM values. The data obtained excluded the presence of current infectious diseases and helminthiasis in the patient.

Results of instrumental research methods. An ECG: heart rate — 65 beats/min; ectopic atrial rhythm, incomplete blockade of the right bundle branch, impaired repolarization (the detected changes were regarded as functional). An X-ray of the lumbar spine in two projections: a lumbar lordosis is preserved, the height of the intervertebral discs is not changed; the ratio of the posterior parts of the vertebrae and the shape of the vertebral bodies are not disturbed; At the lower contour of the spinous process of LIII, an additional shadow of bone density measuring 5×3 mm with clear contours and a homogeneous structure (unfused ossification core) is determined. An ultrasound of the kidneys revealed hyperechogenicity of the cortical layer, characteristic of kidney disease. A bladder data without pathology.

For the first two days, the patient received treatment in the intensive care unit, where intravenous infusion of glucose-saline solutions was carried out, then he was transferred to the nephrology department, where detoxification therapy continued. Discharged on the 14th day of hospitalization with improvement in clinical and laboratory parameters under the supervision of a local pediatrician and nephrologist, genetic consultation was recommended, planned hospitalization in the nephrology department in a year, exemption from physical education for a month, then classes are possible after monitoring kidney function and permission from a sports doctor .

This example demonstrates a typical clinical picture of rhabdomyolysis, complicated by AKI, in a teenager of high physical development, which arose as a result of excessive physical activity during sports activities. Considering the anamnestic data on previously observed long-term myalgia after heavy physical activity, hereditary causes of the disease cannot be excluded. The triggers for rhabdomyolysis could be the asymptomatic course of the infectious disease and the presence of dyslipidemia. A feature of the developed AKI was the absence of a decrease in nitrogen excretion function and the rapid recovery of GFR against the background of detoxification and rehydration therapy. Laboratory manifestations of hypoxia, toxic hepatitis and cholestasis reflected the severity of endotoxemia caused by rhabdomyolysis.

CONCLUSION

Rhabdomyolysis associated with physical activity (post-exercise) in children and adolescents is non-traumatic in origin, often due to hereditary causes and provoked against the background of infectious diseases and metabolic disorders. The acute kidney damage is a typical potentially reversible complication of rhabdomyolysis and requires differential diagnosis, timely adequate treatment and subsequent follow-up of patients to prevent the development of chronic kidney pathology [43].

ADDITIONAL INFORMATION

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

REFERENCES

1. Masolitin S.V., Procenko D.N., Tyurin I.N. i dr. Sovremennyj vzglyad na primenenie metodov ekstrakorporal'noj detoksikacii dlya pri rabdomiolize (obzor). [A modern view on the use of extracorporeal detoxification methods in rhabdomyolysis (review).] Obshchaya reanimatologiya. 2022; 18(3): 59–68. DOI: 10.15360/1813-9779-2022-3-59-68. (In Russian).
2. Chalchat E., Charlot K., Garcia-Vicencio S. et al. Circulating microRNAs after a 24-h ultramarathon run in relation to muscle damage markers in elite athletes. Scand J Med Sci Sports. 2021; 31(9): 1782–95. DOI: 10.1111/sms.14000.
3. Kutepov D.E., Fyodorova A.A., Bazhina E.S. i dr. Effektivnost' sistemy cytosorb u bol'nyh rabdomiolizom razlichnoj etiologii. Pilotnoe issledovanie. [Effectiveness of cytosorb system in patients with rhabdomyolysis of different etiologies. Pilot study]. Kremlevskaya medicina. Klinicheskij vestnik. 2021; 2: 29–35. DOI: 10.26269/g87h-2h50. (In Russian).
4. Borisov A.G., Chernov S.A., Potekhin N.P., Romanov V.P. Netravmaticheskij rabdomioliz kak prichina ostrogo povrezhdeniya pochek. [Non-traumatic rhabdomyolysis as a cause of acute kidney injury]. Nefrologiya. 2019; 23(prilozhenie 1): 44–54. DOI: 10.36485/1561-6274-2019-23-5-44-54. (In Russian).

5. Bobrysheva A.V., Kryuger E.A., Rymarenko N.V., Shchedrova O.V. Osobennosti techeniya nasledstvenno-obuslovlennogo rabdomioliza u podrostka v praktike infekcionista. [Features of the course of hereditary rhabdomyolysis in a teenager in the practice of an infectious disease specialist]. Tavricheskij mediko-biologicheskij vestnik. 2021; 24(4): 42–9. DOI: 10.37279/2070-8092-2021-24-4-42-50. (In Russian).
6. Park Y.S., Song J.Y., Kim S.Y., Kim S.H. Clinical Characteristics of Rhabdomyolysis in Children: Single Center Experience. Child Kidney Dis. 2018; 22(2): 52–7. DOI: 10.3339/jkspn.2018.22.2.52.
7. Mannix R., Tan M.L., Wright R., Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics. 2006; 118: 2119–25 DOI: 10.1542/peds.2006-1352.
8. Pas'ko V.G., Ardashev V.N., Kotenok O.N. i dr. Kompleksnaya terapiya sepsisa, oslozhnennogo razvitiem massivnogo rabdomioliza. [Complex therapy of sepsis complicated by the development of massive rhabdomyolysis]. Lechenie i profilaktika. 2019; 9(2): 63–8. (In Russian).
9. Stahl K., Rastelli E., Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020; 267(4): 877–82. DOI: 10.1007/s00415-019-09185-4.
10. Albaba I., Chopra A., Al-Tarbsheh A.H. et al. Incidence, risk factors, and outcomes of rhabdomyolysis in hospitalized patients with COVID-19 infection. Cureus. 2021; 13(11): e19802. DOI: 10.7759/cureus.19802.
11. Musumeci O., Ferlazzo E., Rodolico C. et al. A Family With a Complex Phenotype Caused by Two Different Rare Metabolic Disorders: GLUT1 and Very-Long-Chain Fatty Acid Dehydrogenase (VLCAD) Deficiencies. Front. Neurol. 2020; 11: 514. DOI: 10.3389/fneur.2020.00514.
12. Alaygut D., Torun Bayram M., Kasap B. et al. Rhabdomyolysis with different etiologies in childhood. World J Clin Pediatr. 2017; 6(4): 161–8. DOI: 10.5409/wjcp.v6.i4.161.
13. Katz J., Labilloy A., Lee A. Recurrent, non-traumatic, non-exertional rhabdomyolysis after immunologic stimuli in a healthy adolescent female: a case report. BMC Pediatr. 2022; 22(1): 515. DOI: 10.1186/s12887-022-03561-2.
14. Schnadthorst P.G., Schulze C., Grunwald M. Sportmedizinische Beratung nach akuter Rhabdomyolyse bei erblicher Myopathie — eine herausfordernde Leistungsdiagnostik. Dtsch Med Wochenschr. 2022; 147(8): 481–4. DOI: 10.1055/a-1769-9073.
15. Tong K., Yu G.S. Acute recurrent rhabdomyolysis in a Chinese boy associated with a novel compound heterozygous LPIN1 variant: a case report. BMC Neurol. 2021; 21(1): 42. DOI: 10.1186/s12883-021-02050-w.
16. Donskoj D.N., Mstislavskaya S.A. Rabdomioliz kak prichina ostrogo povrezhdeniya pochek. [Rhabdomyolysis as a cause of acute kidney injury]. Innovacionnaya nauka. 2021, 7: 148. (In Russian).
17. Zach C., Unterkofler K., Fraunberger P. et al Unrecognized High Occurrence of Genetically Confirmed Hereditary Carnitine Palmitoyltransferase II Deficiency in an Austrian Family Points to the Ongoing Underdiagnosis of the Disease. Front Genet. 2019; 10: 497. DOI: 10.3389/fgene.2019.00497.
18. Fatehi F., Okhovat A.A., Nilipour Y. et al. Adult onset Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD). Eur J Neurol. 2020; 27(11): 2257–66. DOI: 10.1111/ene.14402.
19. Sabinina T.S., Soldatova E.Yu., Melekhina E.V. Rabdomioliz pri ostryh respiratornyh infekciyah u detej. Klinicheskij sluchaj. [Rhabdomyolysis in acute respiratory infections in children. A clinical case]. Infekcionnye bolezni. 2022; 20(4): 108–19. DOI: 10.20953/1729-9225-2022-4-108-119. (In Russian).
20. Berdnikov G.A., Kudryashova N.E., Migunova E.V. i dr. Razvitie rabdomioliza v otdalennom periode perenesennoj novoj koronavirusnoj infekcii COVID-19 (klinicheskoe nablyudenie). [Development of rhabdomyolysis in the long-term period of a new coronavirus infection COVID-19 (clinical observation)]. Zhurnal im. N.V. Sklifosovskogo Neotlozhnaya medicinskaya pomoshch'. 2021; 10(3): 452–9. DOI: 10.23934/2223-9022-2021-10-3-452-459. (In Russian).
21. Hannah J.R., Ali S.S., Nagra D. et al. Skeletal muscles and Covid-19: a systematic review of rhabdomyolysis and myositis in SARS-CoV-2 infection. Clin Exp Rheumatol. 2022; 40(2): 329–38. DOI: 10.55563/clinexprheumatol/mkfmxt.
22. Lee I.H., Ahn D.J. Rhabdomyolysis and acute kidney injury associated with Salmonella infection: a report of 2 cases. Am J Case Rep. 2022; 23: e936407. DOI: 10.12659/AJCR.936407.
23. Galenko S.G., Ohotnikova K.D., Ivanov A.A. i dr. Klinicheckij sluchaj gipokaliemii, oslozhnennoj razvitiem rabdomioliza. [A clinical case of hypokalemia complicated by the development of rhabdomyolysis]. University Therapeutic Journal. 2022; 4(3): 30–8. (In Russian).
24. Rangan G.K., Dorani N., Zhang M.M. et al. Clinical characteristics and outcomes of hyponatraemia associated with oral water intake in adults: a systematic review. BMJ Open. 2021; 11(12): e046539. DOI: 10.1136/bmjopen-2020-046539.

25. Shabunin A.V., Loginov S.P., Drozdov P.A. i dr. Sluchaj rabdomioliza posle naznacheniya atorvastatina recipientu pechenochnogo transplantata, nahodyashchemusya na immunosupressivnoj terapii ciklosporinom. [A case of rhabdomyolysis after administration of atorvastatin to a liver transplant recipient undergoing immunosuppressive therapy with cyclosporine]. Transplantologiya. 2021; 13(2): 158–64. DOI: 10.23873/2074-0506-2021-13-2-158-164.
26. Ionov S.N., Dolbnya A.A., Mihajlova V.A., Zaikina O.A. Zlokachestvennaya gipertermiya. [Malignant hyperthermia]. Sovremennye problemy nauki i obrazovaniya. 2022; 2: 147. (In Russian).
27. Moiseev S.V., Bulanov N.M. Ostroe ili progressiruyushchee uhudshenie funkcii pochek pri immunovospalitel'nyh revmaticheskih zabolevaniyah. [Acute or progressive deterioration of kidney function in immuno-inflammatory rheumatic diseases]. Klin farmakol ter 2023; 32(1): 4–13. (In Russian).
28. Sokolova S.L., Dolgova O.B., Yakunina I.V. Diagnostika sindroma pozicionnogo sdavleniya v toksikologicheskoj i sudebno-medicinskoj prakticheskoj deyatel'nosti. [Diagnosis of positional compression syndrome in toxicological and forensic practice]. Ural'skij medicinskij zhurnal. 2017; 3(147): 137–42. (In Russian).
29. Teplova T.N. Rabdomioliz v klinicheskoj praktike. [Rhabdomyolysis in clinical practice]. Vyatskij medicinskij vestnik. 2016; 4(52): 37–45. (In Russian).
30. Volkov E.V., Gurov A.Yu, Fisher V.V., Batchaeva L.H. Sluchaj okazaniya medicinskoj pomoshchi pacientu s netipichnym debyutom sindroma travmaticheskogo rabdomioliza. [A case of providing medical care to a patient with an atypical onset of traumatic rhabdomyolysis syndrome]. Sibirskoe medicinskoe obozrenie. 2020; (2): 98–102. DOI: 10.20333/2500136-2020-2-98-102. (In Russian).
31. Zamorskij I.I., Unguryan T.N., Mel'nichuk S.P. Antioksidantnaya aktivnost' ceruloplazmina v usloviyah rabdomioliz-inducirovannogo ostrogo povrezhdeniya pochek. [Antioxidant activity of ceruloplasmin in conditions of rhabdomyolysis-induced acute kidney injury]. Biofizika. 2019; 64(6): 1221–4. DOI: 10.1134/S000630291905022X. (In Russian).
32. Fyodorova A.A., Kutepov D.E., Zubarev A.V. i dr. Rabdomioliz: chto novogo v diagnostike i lechenii? [Rhabdomyolysis: what's new in diagnosis and treatment?] Kremlevskaya medicina. Klinicheskij vestnik. 2020; 2: 102–9. DOI: 10.26269/4n94-0746. (In Russian).
33. Omarova H.S., Sajlanova D.K. Rabdomioliz, svyazannyj s fizicheskoj nagruzkoj u lic molodogo vrzrasta (klinicheskij sluchaj). [Rhabdomyolysis associated with physical activity in young people (clinical case)]. Vestnik Kazahskogo nacional'nogo medicinskogo universiteta. 2022; 1: 90–3. (In Russian).
34. Chalchat E., Charlot K., Garcia-Vicencio S. et al. Circulating microRNAs after a 24-h ultramarathon run in relation to muscle damage markers in elite athletes. Scand J Med Sci Sports. 2021; 31(9): 1782–95. DOI: 10.1111/sms.14000.
35. Evdokimova N.E., Cygankova O.V., Latynceva L.D. Sindrom povyshennoj kreatinfosfokinazy plazmy kak diagnosticheskaya dilemma. [Elevated plasma creatine phosphokinase syndrome as a diagnostic dilemma]. RMZH. 2021; 2: 18–25. (In Russian).
36. Zhurkova N.V., Vashakmadze N.D., Surkov A.N. i dr. Selimzyanova L.R. Narusheniya mitohondrial'nogo beta-okisleniya zhirnyh kislot u detej: obzor literatury. [Disorders of mitochondrial beta-oxidation of fatty acids in children: literature review]. Voprosy sovremennoj pediatrii. 2022; 21(6S): 522–8. DOI: 10.15690/vsp.v21i6S.2503. (In Russian).
37. Bugun O.V., Martynovich N.N., Bogonosova G.P. i dr. Nasledstvennye bolezni obmena: aminoacidopatii, organicheskie acidemii, defekty mitohondrial'nogo β-okisleniya. Kratkij obzor. [Hereditary metabolic diseases: aminoacidopathies, organic acidemia, defects of mitochondrial β-oxidation]. Acta biomedica scientifica. 2021; 6(5): 112–25. DOI: 10.29413/ABS.2021-6.5.11. (In Russian).
38. Fyodorova A.A., Kutepov D.E., Zubarev A.V. i dr. Ocenka struktury 4-h glavoj myshcy bedra u pacientki s rabdomiolizom. [Evaluation of the structure of the 4-chapter thigh muscle in a patient with rhabdomyolysis]. Lechenie i profilaktika. 2019; 9(4): 87–91. (In Russian).
39. Emel'yancev A.A., Bardakov S.N., Bojkov I.V. i dr. Elastografiya sdvigovoj volny v diagnostike rabdomioliza. [Shear wave elastography in the diagnosis of rhabdomyolysis]. Izvestiya Rossijskoj Voenno-medicinskoj akademii. 2022; 41(1): 23–30. DOI: 10.17816/rmmar104383. (In Russian).
40. Emel'yancev A.A., Zheleznyak I.S., Bardakov S.N. i dr. MR-relaksometriya v diagnostike rabdomioliza. [MR-relaxometry in the diagnosis of rhabdomyolysis]. REJR 2021; 11(1): 191–9. DOI: 10.21569/2222-7415-2021-11-1-191-199. (In Russian).
41. Emel'yancev A.A., Zheleznyak I.S., Bardakov S.N. i dr. Klinicheskij sluchaj ostrogo postnagruzochnogo rabdomioliza verhnih konechnostej. [A clinical case of acute post-loading rhabdomyolysis of the upper extremities]. Radiologiya — Praktika. 2019; 6(78): 103–14. (In Russian).

42. Golubev V.N., Korolev Yu.N., Murgaeva N.V., Strel'cova K.G. Adaptivnye reakcii organizma cheloveka na vozdejstvie gipoksii. [Adaptive reactions of the human body to the effects of hypoxia]. Izvestiya Rossijskoj voenno-medicinskoj akademii. 2019; 38(3): 178–82.
43. Gaut J.P., Liapis H. Acute kidney injury pathology and pathophysiology: a retrospective review. Clin Kidney J. 2020; 14(2): 526–36. DOI: 10.1093/ckj/sfaa142. (In Russian).

ЛИТЕРАТУРА

1. Масолитин С.В., Проценко Д.Н., Тюрин И.Н. и др. Современный взгляд на применение методов экстракорпоральной детоксикации при рабдомиолизе (обзор). Общая реаниматология. 2022; 18 (3): 59–68. DOI: 10.15360/1813-9779-2022-3-59-68.
2. Chalchat E., Charlot K., Garcia-Vicencio S. et al. Circulating microRNAs after a 24-h ultramarathon run in relation to muscle damage markers in elite athletes. Scand J Med Sci Sports. 2021; 31(9): 1782–95. DOI: 10.1111/sms.14000.
3. Кутепов Д.Е., Фёдорова А.А., Бажина Е.С. и др. Эффективность системы cytosorb у больных рабдомиолизом различной этиологии. Пилотное исследование. Кремлевская медицина. Клинический вестник. 2021; 2: 29–35. DOI: 10.26269/g87h-2h50.
4. Борисов А.Г., Чернов С.А., Потехин Н.П., Романов В.П. Нетравматический рабдомиолиз как причина острого повреждения почек. Нефрология. 2019; 23(приложение 1): 44–54. DOI: 10.36485/1561-6274-2019-23-5-44-54.
5. Бобрышева А.В., Крюгер Е.А., Рымаренко Н.В., Щедрова О.В. Особенности течения наследственно-обусловленного рабдомиолиза у подростка в практике инфекциониста. Таврический медико-биологический вестник. 2021; 24(4): 42–9. DOI: 10.37279/2070-8092-2021-24-4-42-50.
6. Park Y.S., Song J.Y., Kim S.Y., Kim S.H. Clinical Characteristics of Rhabdomyolysis in Children: Single Center Experience. Child Kidney Dis. 2018; 22(2): 52–7. DOI: 10.3339/jkspn.2018.22.2.52.
7. Mannix R., Tan M.L., Wright R., Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics. 2006; 118: 2119–25. DOI: 10.1542/peds.2006-1352.
8. Пасько В.Г., Ардашев В.Н., Котенок О.Н. и др. Комплексная терапия сепсиса, осложненного развитием массивного рабдомиолиза. Лечение и профилактика. 2019; 9(2): 63–8.
9. Stahl K., Rastelli E., Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020; 267(4): 877–82. DOI: 10.1007/s00415-019-09185-4.
10. Albaba I., Chopra A., Al-Tarbsheh A.H. et al. Incidence, risk factors, and outcomes of rhabdomyolysis in hospitalized patients with COVID-19 infection. Cureus. 2021; 13(11): e19802. DOI: 10.7759/cureus.19802.
11. Musumeci O., Ferlazzo E., Rodolico C. et al. A Family With a Complex Phenotype Caused by Two Different Rare Metabolic Disorders: GLUT1 and Very-Long-Chain Fatty Acid Dehydrogenase (VLCAD) Deficiencies. Front. Neurol. 2020; 11: 514. DOI: 10.3389/fneur.2020.00514.
12. Alaygut D., Torun Bayram M., Kasap B. et al. Rhabdomyolysis with different etiologies in childhood. World J Clin Pediatr. 2017; 6(4): 161–8. DOI: 10.5409/wjcp.v6.i4.161.
13. Katz J., Labilloy A., Lee A. Recurrent, non-traumatic, non-exertional rhabdomyolysis after immunologic stimuli in a healthy adolescent female: a case report. BMC Pediatr. 2022; 22(1): 515. DOI: 10.1186/s12887-022-03561-2.
14. Schnadthorst P.G., Schulze C., Grunwald M. Sportmedizinische Beratung nach akuter Rhabdomyolyse bei erblicher Myopathie — eine herausfordernde Leistungsdiagnostik. Dtsch Med Wochenschr. 2022; 147(8): 481–4. DOI: 10.1055/a-1769-9073.
15. Tong K., Yu G.S. Acute recurrent rhabdomyolysis in a Chinese boy associated with a novel compound heterozygous *LPIN1* variant: a case report. BMC Neurol. 2021; 21(1): 42. DOI: 10.1186/s12883-021-02050-w.
16. Донской Д.Н., Мстиславская С.А. Рабдомиолиз как причина острого повреждения почек. Инновационная наука. 2021, 7: 148.
17. Zach C., Unterkofler K., Fraunberger P. et al. Unrecognized High Occurrence of Genetically Confirmed Hereditary Carnitine Palmitoyltransferase II Deficiency in an Austrian Family Points to the Ongoing Underdiagnosis of the Disease. Front Genet. 2019; 10: 497. DOI: 10.3389/fgene.2019.00497.
18. Fatehi F., Okhovat A.A., Nilipour Y. et al. Adult onset Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD). Eur J Neurol. 2020; 27(11): 2257–66. DOI: 10.1111/ene.14402.
19. Сабинина Т.С., Солдатова Е.Ю., Мелехина Е.В. Рабдомиолиз при острых респираторных инфекциях у детей. Клинический случай. Инфекционные болезни. 2022; 20(4): 108–19. DOI: 10.20953/1729-9225-2022-4-108-119.
20. Бердников Г.А., Кудряшова Н.Е., Мигунова Е.В. и др. Развитие рабдомиолиза в отдаленном периоде перенесенной новой коронавирусной инфекции COVID-19 (клиническое наблюдение). Журнал им. Н.В. Склифосовского Неотложная

медицинская помощь. 2021; 10(3): 452–9. DOI: 10.23934/2223-9022-2021-10-3-452-459.
21. Hannah J.R., Ali S.S., Nagra D. et al. Skeletal muscles and Covid-19: a systematic review of rhabdomyolysis and myositis in SARS-CoV-2 infection. Clin Exp Rheumatol. 2022; 40(2): 329–38. DOI: 10.55563/clinexprheumatol/mkfmxt.
22. Lee I.H., Ahn D.J. Rhabdomyolysis and acute kidney injury associated with Salmonella infection: a report of 2 cases. Am J Case Rep. 2022; 23: e936407. DOI: 10.12659/AJCR.936407.
23. Галенко С.Г., Охотникова К.Д., Иванов А.А. и др. Клинический случай гипокалиемии, осложненной развитием рабдомиолиза. University Therapeutic Journal. 2022; 4(3): 30–8.
24. Rangan G.K., Dorani N., Zhang M.M. et al. Clinical characteristics and outcomes of hyponatraemia associated with oral water intake in adults: a systematic review. BMJ Open. 2021; 11(12): e046539. DOI: 10.1136/bmjopen-2020-046539.
25. Шабунин А.В., Логинов С.П., Дроздов П.А. и др. Случай рабдомиолиза после назначения аторвастатина реципиенту печеночного трансплантата, находящемуся на иммуносупрессивной терапии циклоспорином. Трансплантология. 2021; 13(2): 158–64. DOI: 10.23873/2074-0506-2021-13-2-158-164.
26. Ионов С.Н., Долбня А.А., Михайлова В.А., Заикина О.А. Злокачественная гипертермия. Современные проблемы науки и образования. 2022; 2: 147.
27. Моисеев С.В., Буланов Н.М. Острое или прогрессирующее ухудшение функции почек при иммуновоспалительных ревматических заболеваниях. Клин фармакол тер 2023; 32(1): 4–13.
28. Соколова С.Л., Долгова О.Б., Якунина И.В. Диагностика синдрома позиционного сдавления в токсикологической и судебно-медицинской практической деятельности. Уральский медицинский журнал. 2017; 3(147): 137–42.
29. Теплова Т.Н. Рабдомиолиз в клинической практике. Вятский медицинский вестник. 2016; 4(52): 37–45.
30. Волков Е.В., Гуров А.Ю., Фишер В.В., Батчаева Л.Х. Случай оказания медицинской помощи пациенту с нетипичным дебютом синдрома травматического рабдомиолиза. Сибирское медицинское обозрение. 2020; (2): 98–102. DOI: 10.20333/2500136-2020-2-98-102.
31. Заморский И.И., Унгурян Т.Н., Мельничук С.П. Антиоксидантная активность церулоплазмина в условиях рабдомиолиз-индуцированного острого повреждения почек. Биофизика. 2019; 64(6): 1221–4. DOI: 10.1134/S000630291905022X.
32. Фёдорова А.А., Кутепов Д.Е., Зубарев А.В. и др. Рабдомиолиз: что нового в диагностике и лечении? Кремлевская медицина. Клинический вестник. 2020; 2: 102–9. DOI: 10.26269/4n94-0746.
33. Омарова Х.С., Сайланова Д.К. Рабдомиолиз, связанный с физической нагрузкой у лиц молодого врзраста (клинический случай). Вестник Казахского национального медицинского университета. 2022; 1: 90–3.
34. Chalchat E., Charlot K., Garcia-Vicencio S. et al. Circulating microRNAs after a 24-h ultramarathon run in relation to muscle damage markers in elite athletes. Scand J Med Sci Sports. 2021; 31(9): 1782–95. DOI: 10.1111/sms.14000.
35. Евдокимова Н.Е., Цыганкова О.В., Латынцева Л.Д. Синдром повышенной креатинфосфокиназы плазмы как диагностическая дилемма. РМЖ. 2021; 2: 18–25.
36. Журкова Н.В., Вашакмадзе Н.Д., Сурков А.Н. и др. Нарушения митохондриального бета-окисления жирных кислот у детей: обзор литературы. Вопросы современной педиатрии. 2022; 21(6S): 522–8. DOI: 10.15690/vsp.v21i6S.2503.
37. Бугун О.В., Мартынович Н.Н., Богоносова Г.П. и др. Наследственные болезни обмена: аминоацидопатии, органические ацидемии, дефекты митохондриального β-окисления. Краткий обзор. Acta biomedica scientifica. 2021; 6(5): 112–5. DOI: 10.29413/ABS.2021-6.5.11.
38. Фёдорова А.А., Кутепов Д.Е., Зубарев А.В. и др. Оценка структуры 4-х главой мышцы бедра у пациентки с рабдомиолизом. Лечение и профилактика. 2019; 9(4): 87–91.
39. Емельянцев А.А., Бардаков С.Н., Бойков И.В. и др. Эластография сдвиговой волны в диагностике рабдомиолиза. Известия Российской Военно-медицинской академии. 2022; 41(1): 23–30. DOI: 10.17816/rmmar104383.
40. Емельянцев А.А., Железняк И.С., Бардаков С.Н. и др. МР-релаксометрия в диагностике рабдомиолиза. REJR 2021; 11(1): 191–9. DOI: 10.21569/2222-7415-2021-11-1-191-199.
41. Емельянцев А.А., Железняк И.С., Бардаков С.Н. и др. Клинический случай острого постнагрузочного рабдомиолиза верхних конечностей. Радиология — Практика. 2019; 6(78): 103–14.
42. Голубев В.Н., Королев Ю.Н., Мургаева Н.В., Стрельцова К.Г. Адаптивные реакции организма человека на воздействие гипоксии. Известия Российской военно-медицинской академии. 2019; 38(3): 178–82.
43. Gaut J.P., Liapis H. Acute kidney injury pathology and pathophysiology: a retrospective review. Clin Kidney J. 2020; 14(2): 526–36. DOI: 10.1093/ckj/sfaa142.

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RUSLAN ABDULLAEVICH NASYROV (ON THE OCCASION OF THE 70TH BIRTHDAY)

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РУСЛАН АБДУЛЛАЕВИЧ НАСЫРОВ (К 70-ЛЕТИЮ СО ДНЯ РОЖДЕНИЯ)

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November 11, 2023 marks the 70th anniversary of Ruslan Abdullaevich Nasyrov, one of the leading modern scientists in the field of pathological anatomy of childhood diseases and infectious pathology, professor, doctor of medical sciences, head of the department of pathological anatomy with a course of forensic medicine named after. Professor D.D. Lokhov, vice-rector for scientific work of the St. Petersburg State Pediatric Medical University of the Ministry of Healthcare of the Russian Federation (SPbSPMU).

Ruslan Abdullaevich devoted more than 50 years to scientific activity in pathomorphology, an interest in which arose while still a student under the leadership of the head of the Department of Human Anatomy of the Semipalatinsk State Medical Institute, Professor E.P. Tsvetova. The main development of Ruslan Abdullaevich as a specialist and scientist was in the department of pathological anatomy of the Institute of Experimental Medicine of the USSR Academy of Medical Sciences, which was headed by Professor V.E. Pigarevsky. In 1984, Ruslan Abdullaevich successfully defended his Ph.D. thesis on the topic "The state of neurons of the spinal nodes and spinal cord during hypokinesia" (scientific advisor Professor G.V. Konovalov), in 1995 — his doctoral dissertation on the topic "Patomorphology and issues of the pathogenesis of herpetic infection brain" (scientific consultant Professor V.P. Tumanov). While still working on his doctoral dissertation, in 1989 R.A. Nasyrov headed the pathomorphological group of the Scientific Research Institute of Childhood Infections.

The pediatric profile of scientific interests naturally continued when in 2007 Ruslan Abdullaevich

moved to the St. Petersburg State Pediatric Medical Academy to the position of head of the department of pathological anatomy (since 2009 — the department of pathological anatomy with a course of forensic medicine). In 2010, R.A. Nasyrov was appointed vice-rector for scientific work. Ruslan Abdullaevich is a member of the Presidium of the Russian Society of Pathologists, a member of the certification commission on pathological anatomy, and deputy editor-in-chief of the Pediatrician magazine, which is included in the list of scientific journals and publications of the Higher Attestation Commission. During the period 2009–2019, R.A. Nasyrov was the chief specialist in pathomorphology of childhood diseases of the Healthcare Committee of St. Petersburg.

Ruslan Abdullaevich honors his teachers and carefully preserves the traditions of his predecessors. On the initiative of R.A. Nasyrov at the end of 2022, the Department of Pathological Anatomy with a course of Forensic Medicine was named after its founder, the founder of the St. Petersburg School of Children's Pathologists, Professor Dmitry Dmitrievich Lokhov. R.A. Nasyrov is sincerely devoted to science; he is a talented leader, teacher and doctor. Ruslan Abdullaevich raised morphological research at the university to a new level by organizing an immunohistochemical (IHC) laboratory at his department.

Professor R.A. Nasyrov created a modern scientific and practical school of pathological anatomy, perinatal pathology and childhood diseases, which provides advisory assistance to doctors and patients in all regions of the Russian Federation. Under the leadership of Ruslan Abdullaevich, meetings of the section of pediatric pathology of the St. Petersburg Society of Pathologists are held; since 2018, within the framework of the congress "Healthy Children — the Future of the Country", conferences of pediatric pathologists have been organized, in which pathologists and forensic experts participate with scientific reports from various regions of Russia and foreign countries.

Ruslan Abdullaevich Nasyrov makes a great contribution to the training of medical, teaching and research personnel for the whole of Russia, to the development of domestic pathological anatomy. R.A. Nasyrov opened the way to science and practical medicine to many of his students, who continue his work in different parts of the world. He and his students identified immunohistochemical markers for the diagnosis and prognosis of diphtheria, chronic tonsillitis, infectious mononucleosis, viral hepatitis, tuberculosis, HIV infection, erythroderma, sudden death syndrome in children, and pathology of the gastrointestinal tract. For the first time R.A. Nasyrov, during an immunohistochemical study, discovered the bovine leukemia virus antigen in certain forms of breast cancer, and obtained original data on the significance of the infectious factor in ovarian cancer. Based on the study of a wide range of immunohistochemical markers of chronic endometritis, effective tactics for restoring reproductive function in women with a burdened obstetric and gynecological history have been developed, which can significantly affect the increase in the total fertility rate in Russia. The research by Professor R.A. Nasyrov and his students showed that the structures of the microvasculature vessel wall are the earliest target of the influence of pathogenicity factors during herpetic neuroviral infection. Subsequently, the dominant role of the vascular factor was shown using examples of bacterial (Haemophilus influenzae, pneumococcal) and fungal (cryptococcal) infections. The results obtained were of fundamental importance and determined a new scientific direction in the study of the role of the microvasculature vessel wall in the pathogenesis of infectious diseases. These data brought new insights into the understanding of the genesis and treatment tactics of infectious diseases, as well as into the further development of the theory of pathology.

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Ruslan Abdullaevich, having a wealth of clinical experience, is directly involved in the diagnostic work of the pathology department of the university, conducting clinical and anatomical analyzes of each fatal case, which contributes to the solution of an urgent problem — the study of the causes and mechanisms of death in perinatal pathology and pathology of childhood.

The results of Ruslan Abdullaevich's work are reflected in monographs, guidlines and manuals, among them "Diphtheria in Children" (2000), "Viral meningitis and meningoencephalitis in children" (2008), "Purulent meningitis in children" (2017), "Pathoanatomical diagnosis in perinatology "(2019), "Pathomorphological studies in perinatology" (2020), etc. The total number of scientific works exceeds 300 publications, of which more than 100 were published over the past five years, with 32 works in journals from the Scopus list. With the participation and guidance of R.A. Nasyrov, over the past three years, published the textbook "Pathological Anatomy. General part" (2021), 6 manuals (one of them published in Germany), 12 teaching aids. Professor R.A. Nasyrov is a co-author of 14 patents for inventions. Under his leadership, 14 candidate and 3 doctoral dissertations were defended. Currently, 4 candidate and 1 doctoral dissertations are being carried out.

For achievements in the field of higher education, Professor R.A. Nasyrov in 2020 was awarded the gratitude of the Legislative Assembly of St. Petersburg. In 2022, at the Congress of Russian Pathologists he was awarded a diploma for his significant contribution to the development of pathological anatomy and active participation in the work of the Russian Society of Pathologists, in 2023 he became a laureate of the national award of the Russian Professorial Assembly "Vice-Rector of the Year for Research" in the category of medical universities.

The staff of the Department of Pathological Anatomy with the Course of Forensic Medicine named after. Professor D.D. Lokhov, the editorial board of the journal "Children's Medicine of the North-West", students and colleagues cordially congratulate Ruslan Abdullaevich on his anniversary and wish him good health, successful creative search, new scientific discoveries and professional achievements.

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TO THE ANNIVERSARY OF EVGENIA VIKTOROVNA BOYTSOVA

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К ЮБИЛЕЮ ЕВГЕНИИ ВИКТОРОВНЫ БОЙЦОВОЙ

© **Коллектив кафедры пропедевтики детских болезней с курсом общего ухода за детьми**

Для цитирования: Коллектив кафедры пропедевтики детских болезней с курсом общего ухода за детьми. К юбилею Евгении Викторовны Бойцовой // Children's medicine of the North-West. 2023. T. 11. № 4. C. 129–130. DOI: https://doi.org/10.56871/CmN-W.2023.15.27.016

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On the last day of the outgoing year, Evgenia Viktorovna Boytsova, a professor at the Department of Propaedeutics of Children's Diseases with a course in general child care, celebrates her anniversary.

She was born on December 31, 1953 in Penza in the family of an engineer and a military man. In 1970 she graduated from high school in Petropavlovsk-Kamchatsky, in 1977 she graduated from the Leningrad Pediatric Institute with a degree in Pediatrics. In 1977–1978 she studied as an internship, then she worked as a local doctor in a children's clinic. In 1980–1982 she studied in clinical residency in the specialty "Pulmonology" at the Leningrad Research Institute of Pulmonology under the guidance of professors A.V. Bogdanova and K.F. Shiryaeva.

After residency, Evgeniya Viktorovna worked as a pediatric pulmonologist in the children's pulmonology department of the Pulmonology Research Institute. In 1987 she was elected to the position of junior researcher at the laboratory of pediatric pulmonology at the Research Institute of Pulmonology. In 1993 she defended her candidate's thesis on the topic "Underdevelopment of the lungs in children", in 2003 she defended her doctoral dissertation on the topic "Bronchiolitis obliterans in children (clinical, functional and radiological features)" under the scientific advice of Professor A.V. Bogdanova. In her dissertation, for the first time in our country, the clinical and functional features of the disease were studied in detail and diagnostic criteria were developed based on modern radiological and functional methods. Until 2019 Evgenia Viktorovna worked at the Research Institute of Pulmonology of the St. Petersburg State Medical University named after academician I.P. Pavlov as a leading researcher and part-time at St. Petersburg State Pediatric Medical University she works as a professor in the department of propaedeutics of children's diseases with a course of general child care. Evgenia Viktorovna has valid certificates in the specialty "Pulmonology" and "Pediatrics". Since 2012 she has been

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a pediatric pulmonologist in the Leningrad region, a consultant at the Children's Regional Clinical Hospital. She observes all complex patients in the regional hospital, conducts clinical analyzes and medical examinations. Her opinion is always authoritative; the staff of the regional hospital treat her with great respect and love.

Evgenia Viktorovna is the author and co-author of more than 350 publications, including co-author of 4 monographs ("Interstitial lung diseases in infants", "Bronchopulmonary dysplasia: from Norsway to the present day", "Pharmacotherapy of chronic obstructive pulmonary diseases in children", "Chronic obstructive pathology lungs in adults and children. A guide for doctors"), 10 educational and teaching aids, more than 50 articles in leading peer-reviewed journals. Hirsch index RSCI — 16. Evgenia Viktorovna took an active part in the preparation of Federal clinical recommendations on bronchopulmonary dysplasia, the scientific and practical program "Bronchopulmonary dysplasia" of the Russian Respiratory Society (RRS), the Russian Association of Perinatal Medicine Specialists (RASPM), the Federation of Pediatricians of the CIS Countries, the Pediatric respiratory society. Currently, an updated clinical guideline on bronchopulmonary dysplasia with her participation is being prepared for publication. Evgenia Viktorovna is also actively involved in creating a national register of patients with cystic fibrosis, and is a member of the RRS, the European Respiratory Society.

Under the guidance of Evgenia Viktorovna, 2 candidate dissertations were completed: "Prevalence and clinical features of bronchial asthma in children of the Leningrad region" (Arestova N.Ya.) and "Outcomes of bronchopulmonary dysplasia in children and adolescents" (Zapevalova E.U.).

Thus, the sphere of scientific interests of Professor E.V. Boitsova's areas of expertise include chronic obstructive pulmonary diseases in children, neonatal pulmonology, neonatology, interstitial diseases of childhood, and cystic fibrosis. Together with other specialists, based on her research, she created and clinically tested a system of staged management of children suffering from bronchopulmonary dysplasia and its complications, established the outcomes of bronchopulmonary dysplasia in older childhood and adolescence, developed an algorithm for diagnosing the consequences of this pathology, and determined its significance for respiratory health in children. older age. For the first time in our country, with the participation of Evgenia Viktorovna, observations of rare diseases, including interstitial lung diseases and genetic syndromes, were published.

An excellent teacher, methodologist, thoughtful and erudite doctor, excellent lecturer, Evgenia Viktorovna enjoys love and respect in the team. She is a comprehensively educated person, knows domestic and foreign literature well, loves to travel, and enjoys gardening. Evgenia Viktorovna has a wonderful, friendly family: a husband, a daughter and an adult grandson. Both colleagues and relatives congratulate Evgenia Viktorovna on her anniversary, wish her health, creative success, and new bright impressions.

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.

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АВТОРСКОЕ ПРАВО

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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 целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. Объем текста авторского резюме определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах 200–250 слов (1500–2000 знаков).

4. **Ключевые слова** (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.

РЕЦЕНЗИРОВАНИЕ

Статьи, поступившие в редакцию, обязательно рецензируются. Если у рецензента возникают вопросы, то статья с комментариями рецензента возвращается Автору. Датой поступления статьи считается дата получения Редакцией окончательного варианта статьи. Редакция оставляет за собой право внесения редакторских изменений в текст, не искажающих смысла статьи (литературная и технологическая правка).

АВТОРСКИЕ ЭКЗЕМПЛЯРЫ ЖУРНАЛА

Редакция обязуется выдать Автору 1 экземпляр Журнала на каждую опубликованную статью вне зависимости от числа авторов. Авторы, проживающие в Санкт-Петербурге, получают авторский экземпляр Журнала непосредственно в Редакции. Иногородним Авторам авторский экземпляр Журнала высылается на адрес автора по запросу от автора. Экземпляры спецвыпусков не отправляются авторам.

АДРЕС РЕДАКЦИИ

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

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

М. Ф. Сухарев, С. Б. Фищев, М. Г. Рожкова

Учебник соответствует программе Министерства здравоохранения Российской Федерации по ортопедической стоматологии, предназначен и будет полезным для преподавателей курсов и стоматологических кафедр, студентов стоматологических факультетов, ординаторов, аспирантов, врачей-стоматологов.

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ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. ОБЩИЙ КУРС

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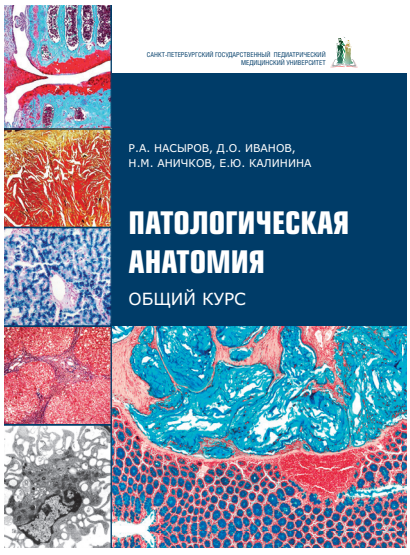

В общем курсе патологической анатомии (клинической патоморфологии) рассмотрены вопросы общей патологической анатомии: методы исследования в патоморфологии, повреждение и гибель клеток и тканей, в том числе старение; нарушения кровообращения и иных сред организма, воспаление, репарация и регенерация, заживление ран, иммунная патология, адаптация, патология роста клеток и их дифференцировки, опухоли, генетические заболевания, учение о диагнозе в патологической анатомии, патология и факторы окружающей среды, патология, вызванная питанием, констатация смерти и др.

Учебник рассчитан на студентов-медиков всех факультетов, а также на врачей, интересующихся вопросами общей патологической анатомии.

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