ISSN 2221-2582

2024
Т. 12 № 3

Children's Medicine of the North-West

Научно-практический медицинский журнал

Основан в 2005 году
Выпускается 4 раза в год

Версия online:
http://ojs3.gpmu.org/index.php/childmed

В номере:

Children's Medicine of the North-West

2024, Volume 12, N 3 Scientific and practical journal

Рецензируемый научно-практический журнал
Children's Medicine of the North-West
(Детская медицина Северо-Запада)

Основан в 2005 году в Санкт-Петербурге

ISSN 2221-2582

Выпускается 4 раза в год

Журнал реферируется РЖ ВИНИТИ

Издатели, учредители:
Федеральное государственное бюджетное образовательное учреждение высшего профессионального образования «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России (адрес: 194100, Санкт-Петербург, Литовская ул., 2)
Фонд НОИ «Здоровые дети — будущее страны» (адрес: 197371, Санкт-Петербург, ул. Парашютная, д. 31, к. 2, кв. 53).

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий имассовых коммуникаций (РОСКОМНАДЗОР) ПИ № ФС77-80534 от 01 марта 2021 г. (ранее ПИ № ФС77-21560 от 12 июля 2005 г.)

Журнал входит в **Перечень ведущих научных журналов и изданий ВАК,** в которых должны быть опубликованы основные результаты диссертаций на соискание ученых степеней кандидата и доктора наук (Распоряжение № 428-р от 11.12.2023).

Проект-макет: Титова Л.А.
Layout project: Titova L.A.

Электронная версия / Electronic version
https://www.gpmu.org/science/pediatrics-magazine/
Chiidmed, http://elibrary.ru

Титова Л.А. (выпускающий редактор)
Варламова И.Н. (верстка)
Titova L.A. (Commissioning Editor)
Varlamova I.N. (layout)

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https://ojs3.gpmu.org/index.php/childmed,
lt2007@inbox.ru

Формат 60×90/8. Усл.-печ. л. 24,5. Тираж 100 экз. Распространяется бесплатно. Оригинал-макет изготовлен ФГБОУ ВО СПбГПМУ Минздрава России.

Format 60×90/8. Cond.-printed sheets 24,5. Circulation 100. Distributed for free. The original layout is made Saint Petersburg State Pediatric Medical University.

Отпечатано ФГБОУ ВО СПбГПМУ Минздрава России.
194100, Санкт-Петербург, Литовская ул., 2.
Заказ 70. Дата выхода 14.10.2024.

Printed by Saint Petersburg State Pediatric Medical University.
2 Lithuania, Saint Petersburg 194100 Russian Federation.
Order 70. Release date 14.10.2024.

СОДЕРЖАНИЕ

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UDC 355.511.512+614.2+347.157+616.1/.4-053.2-036.12+371.71+004.01
DOI: 10.56871/CmN-W.2024.98.73.002

MODERN DIGITAL TECHNOLOGIES FOR ASSESSING "CHILDREN'S SPACE" IN HEALTH AND DISEASE

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For citation: Simakhodsky AS, Shapovalov VV, Petrova NV, Sevostyanova LD, Leonova IA, Simakhodsky OA. Modern digital technologies for assessing "children's space" in health and disease. Children's Medicine of the North-West. 2024;12(3):7–17. DOI: https://doi.org/10.56871/CmN-W.2024.98.73.002

Received: 22.05.2024 **Revised: 28.06.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* Global and Russian phenomena lead to a deterioration in the health of the child population. Evidence is stable levels of morbidity, the torpidity of its structure, the growth of painful diseases, the increase in negative dynamics in the development of reproductive functions and the increase in disability. These processes occur against the background of depopulation processes. The current situation was carefully reviewed at the XXIV Congress of Pediatricians in 2023. *The purpose of the study* is to take a broader look at the medical and social factors that shape health by determining the health indicators of the child population using digital technologies. In recent years 2010–2022. An improvement to the automated systems is the new "children's space" scheme, which demonstrates the level of compliance. *Materials and methods.* The study used data provided by the organizational and methodological center for analysis and prognosis of maternal and child health in the field of health care in St. Petersburg and the Petrostat association. The database was compiled according to Rosstat forms: N 030/u, forms N 12 for children's clinics and N 14 for children's hospitals, forms N 30-PO/o-12, N 30-PO/o-17 based on the results of preventive examinations. The research and mathematical processing were carried out using a telemedicine system (TMS) on the platform of the AKDO APK version, registration certificate N FSR 2009/95279, certified HIMSS Analytics consultant, state certificate N RZN 2019/9419, methods of variation statistics. *Research results.* A multi-level system has been methodologically formed, justifying the concept of "children's space", based on external and internal factors with the child's body. Based on this, the fundamental factors within the country were identified, embedded in the comparative characteristics of the standard of a healthy child and wary. The method of visualization of priority factors (third level) was selected. Completion of the fourth level of preparation for the conducted research. The final (technological) one showed a clear picture of the child's health status, that is, the health of the group.

Keywords: *preventive examinations, incidence of chronic non-infectious diseases (CNCDs), health formation factors, "children's space", rehabilitation (habilitation) of premature infants, digital technologies*

СОВРЕМЕННЫЕ ЦИФРОВЫЕ ТЕХНОЛОГИИ ОЦЕНКИ «ДЕТСКОГО ПРОСТРАНСТВА» В НОРМЕ И ПРИ ПАТОЛОГИИ

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Для цитирования: Симаходский А.С., Шаповалов В.В., Петрова Н.В., Севостьянова Л.Д., Леонова И.А., Симаходский О.А. Современные цифровые технологии оценки «детского пространства» в норме и при патологии // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 7–17. DOI: https://doi.org/10.56871/CmN-W.2024.98.73.002

Поступила: 22.05.2024 **Одобрена: 28.06.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение*. Общемировые и российские тенденции свидетельствуют об ухудшении здоровья детского населения. Доказательствами служат стабильные уровни хронической заболеваемости, торпидность ее структуры, рост психических заболеваний, нарастание отрицательной динамики в становлении репродуктивных функций и рост инвалидности. Указанные процессы протекают на фоне депопуляционных процессов. Сложившаяся ситуация была детально рассмотрена на XXIV Конгрессе педиатров в 2023 году. *Цель исследования*. На основании динамических показателей здоровья детского населения с использованием цифровых технологий шире взглянуть на медико-социальные факторы, формирующие здоровье. За годы наблюдений с 2010 по 2022 с совершенствованием автоматизированных систем предлагается схема «детского пространства», которая свидетельствует об уровне влияния исследуемых факторов. *Материалы и методы*. В исследовании использованы данные, предоставленные Организационно-методическим центром анализа и прогноза здоровья матери и ребенка Комитета по здравоохранению Санкт-Петербурга и объединением «Петростат». База данных сформирована по формам Росстата: № 030/у, формам № 12 по детским поликлиникам и № 14 по детским стационарам, формам № 30-ПО/о-12, № 30-ПО/о-17 по результатам профилактических осмотров. Исследование и математическая обработка проводились с использованием телемедицинской системы (ТМС) на платформе версии АПК «АКДО», регистрационное удостоверение № ФСР 2009/95279, сертифицированный консультант HIMSS Analytics, регистрационное удостоверение № РЗН 2019/9419, методами вариационной статистики. *Результаты исследования*. Методологически сформирована многоуровневая система обоснования концепции «детского пространства», основанная на взаимодействии внешних и внутренних факторов с организмом ребенка. Исходя из этого, были выделены основополагающие факторы влияния, заложенные в сравнительные характеристики эталона здорового ребенка и конкретного пациента. Выбран метод визуализации приоритетных факторов (третий уровень). Четвертый уровень отражает заключение по проведенному исследованию. Завершающий (технологический) уровень показал визуальную картину состояния здоровья ребенка, то есть группу здоровья.

Ключевые слова: *профилактические осмотры, заболеваемость хроническими неинфекционными заболеваниями, факторы формирования здоровья, «детское пространство», реабилитация (абилитация) недоношенных, цифровые технологии*

INTRODUCTION

Over the past five years, negative trends in children's health have been noted at the annual conferences with international participation "Actual problems of paediatrics" [1]. In the last decade, in St. Petersburg, there is an increase in morbidity and disability, persistent nature of its structure, the deterioration of not only somatic but also reproductive health. There is also a high level of mental disorders and deviant behaviour. Organization of prevention and detection of diseases, and control over the implementation of treatment and rehabilitation measures leaves much to be desired. In our opinion, in reforming primary paediatric care, little attention is paid to the introduction of modern digital technologies and parental participation. The developed automated systems help to reduce labour and financial costs, objectify risk

factors in health formation, and specify treatment and preventive measures.

AIM

Based on negative dynamics of most medical and demographic indicators of the child population of St. Petersburg over a period of more than 10 years, to demonstrate the possibilities of a comprehensive assessment of the formation of children's health using digital systems.

MATERIALS AND METHODS

The material for the study was analysis of Rosstat reporting forms N 19 for children's clinics, N 14 for children's hospitals, N 030/u "Control card for dispensary observation". In the study, materials of the meeting of the Coordination Council under the President of the Russian Federation dated 15.11.2016, and the document of Government instructions to ministries and departments dated 21.12.2016 were used. Statistical data were obtained from the Petrostat association and the Organizational and methodological centre for analysis and prognosis of maternal and child health of the Health Committee. Statistical processing was done using methods of variation statistics (Pearson criterion, Fisher's angular transformation criterion).

RESULTS

Historically, in practical and theoretical paediatrics, there are attempts to comprehensively assess health status and development dynamics of both the child population as a whole and a specific child. Specialists accepted certain criteria for examination: genetic characteristics, perinatal and postnatal factors, quality of care, education, medical and social assistance and the environment. These general concepts are realized in the form of regularities of genetic code, physical development (acceleration and retardation), features of intellectual development, aggregate health characteristics (health group), constitutional variants (diathesis) and adaptation to society [2–5]. We have tried to examine dynamical series of certain medical and social indicators both to confirm negative trends and to explore the possibility of developing an unconventional assessment of children's health. The results are presented in Table 1.

Negative trends in the child population are confirmed by the situation in the field of mental and reproductive health ($p < 0.01$), torpid morbidity rates and a significant increase ($p < 0.01$) in disability. An increase in birth rate ($p < 0,01$) since 2018 sharply changes the vector towards negative patterns. The results obtained almost completely correspond to all-Russian trends [6].

Numerous attempts at comprehensive understanding of the processes of health formation have given rise to a significant number of terms: "comfort zone", "childhood territory", "children's space", "illness-health zone" [7, 8]. The subject of consideration is relevant, since in paediatrics it is directly related to growth and development [9, 10]. "Paediatrics as a medical subject is radically different from adult medicine, because paediatrics is a combination of medicine of illnesses and medicine of development. The essence of paediatrics as a science of development can be concentrate in four major parts: protection, provision, adequate stimulation, control and early correction of developmental deviations. Only in paediatrics of development there are keys to prevention of chronic diseases in adults…" (Vorontsov I.M., 2006) [11].

The development of society in the 21st century is associated with the awareness of changes in political and economic systems, a number of problems in education, health care, culture and upbringing. The century of digital technologies allowed medical science and practice to take a broader look at assessing the situation by introducing automated systems for diagnosing disease profiles, compiling prognostic maps, and various therapeutic and rehabilitation schemes. Serious significance is devoted to social and cultural area of a child as an important element of conscious influence on the process of personality formation, which will create the basis for subsequent adaptation to society.

Nowadays, in conditions of globalization, a threat to the world of childhood is significantly increased. And although the Declaration of the Rights of the Child N 1386 published by the United Nations refers to 20.11.1959, children in current global world are not assessed as a prosperous group of the population. There is a lack of positive dynamics, their lives are threatened by various social, political and economic risks. Hunger against the background of abundance, degradation against the background of high cultural achievements, illness and death in the context of rapid scientific, technological and medical progress are observed. The task of rethinking the so-called global childhood, its risks, threats, basic values and status seems extremely

Table 1. Dynamics of some medical and social indicators of the child population of St. Petersburg

Таблица 1. Динамика некоторых медико-социальных показателей детского населения Санкт-Петербурга

№ п/п	Показатели / Indicators	Годы / Years							
		2010	2012	2014	2016	2018	2021	2022	2023
1.	Количество детского населения 0–17 лет (абс.) / Child population 0–17 years old (abs.)	666 200	715 300	781 435	821 979	924 044	947 039	963 262	934 465
2.	Количество детей-инвалидов 0–17 лет, состоящих на учете детских поликлиник / The number of disabled children 0–17 years old registered in children's clinics	15 009	14 830	15 563	16 064	17 143	18 510	19 360	21 014
3.	Общая заболеваемость детей 0–17 лет по данным формы №12 Росстата / General morbidity of children aged 0–17 years according to Rosstat forms N 12	3085,9	3034,5	2931,7	3242,8	3090,8	2838,5	3299,5	3362,5
4.	Уровень психических расстройств и девиантного поведения в структуре инвалидности 0–17 лет (%) / The level of mental disorders and deviant behavior in the structure of disability 0–17 years (%)	3927 (26,2)	4116 (27,8)	4566 (29,3)	5274 (32,8)	5904 (34,4)	6485 (38,0)	6900 (35,6)	7687 (36,6)
5.	Заболеваемость репродуктивной системы детей 0–17 лет / Reproductive system morbidity in children 0–17 years old	16,7	15,5	14,3	23,3	23,4	26,6	26,7	26,9
6.	Коэффициент рождаемости* / Fertility rate*	11,4	12,6	13,1	13,9	11,9	10,3	9,9	9,0
7.	Коэффициент младенческой смертности* / Infant mortality rate*	4,7	4,6	4,3	3,9	3,8	3,4	3,7	4,1

* * Rosstat data. / Данные Росстата.

urgent [12]. A philosophical research on childhood shows the dehumanization of the child's social and cultural space and its living environment. In the International Convention on the Rights of the Child (1989), the child's right to life was recorded. A type of attitude towards the area of childhood and the process of growing up should not be negative, just as it cannot be indifferent. A methodological basis of an examination should scrupulously assess factors that determine the health of a child, which will be the key to more accurate diagnostics and the development of recommendations for treatment and rehabilitation at the technological level [13, 14].

In 2015, the XXII International Conference "Territory of Childhood with Special Educational Needs" identified a high dependence of children on social networks and drug addiction. If the beginning is determined by pampering and the thought "I will definitely quit when I want to," then in the future this bad habit develops into an addiction. Also, a family and friends play an important role. With proper upbringing of a child and parental control, the state of the internal environment and worldview is reinforced, and over time is completely replaced by a person's self-control [15]. Due to this fact, childhood can be viewed as a living archive of previous experience and a fertile field for the emergence of new relationships, concepts and interpersonal connections. The children's environment is represented by the most powerful energy of rela-

tionships and the formation of each child's own worldview [2].

Modern views of paediatrics and developmental psychology on the formation of children's health base on objective approach to assessment of health, personality in its subjective qualities and, above all, as a subject of its own environment, space and relationships with external factors. The concept of "life space" of the individual is correlated with the categories of "life world", "life space", "image of the world", "semiosphere", etc. The relevance of the problem of child's development in social, psychological, and others areas is in the main patterns of the modern concept of "children's space", and also concepts created by psychology of the environment [16].

The European Child and Adolescent Health Strategy 2015–2020, developed by the World Health Organization (WHO), also believes that every child should have an opportunity to live a healthy and fulfilling life. To realise the opportunity, WHO Regional Office for Europe countries have adopted a new strategy, Investing in children: The European child and adolescent health strategy 2015–2020[1].

Moving on to the study of terminology, the most understandable is the term "comfort zone". This term means the life area, which gives feeling of comfort and safety. As a rule, the comfort zone is determined by habitual patterns of behaviour: what you are used to is what you are comfortable with. Simply put, it is a state in which you feel "at ease". What is wrong with comfort and safety? Nothing, except that they make it very difficult to develop and learn new things. Every type of development, education, and formation of resilience is associated with going beyond the boundaries of your comfort zone. Beyond the comfort zone is the risk zone. Reasonable exit beyond the comfort zone into the risk zone is a necessary condition for personal development. As a rule, the younger a person is, the easier and more willing human is to expand the comfort zone [17]. Also, such exit to a certain extent limited by fluctuations in permissible values. This is accepted in paediatrics in the form of centiles, sigma deviations, etc.

In the Russian Federation, in practical children's health care, priority attention is paid to preventive methods at all steps of its development. Systems of early detection of diseases, based on strictly formalized approaches, a long time ago have proven their effectiveness and are widely used in practice. Moreover, one of the first systems of artificial intelligence in the world (Automated complex of dispensary examination systems (ACDES) for multidisciplinary assessment of children's health were created in Russia. To solve problems of such complexity, a special mathematical and software apparatus was created, on the basis of which software packages were built, verified, and demonstrated to be highly medically and economically efficient. Implementation into practice was carried out both under state programs and at the initiative of the heads of medical and preventive institutions (MPI) and regional structures.

Nowadays, automated systems are widely used in conducting preventive examinations and are closely linked with advisory systems on issues of predicting the subsequent condition of each patient. B.A. Kobrinskiy, as an example, cites ACDES in St. Petersburg and DIDENAS in Moscow, which, having a set of programs, are defined as a screening diagnostics system. The formation of groups of varying degrees of risk of developing diseases involved taking into account the degrees of threat and the probable nature of manifestations by type of pathology [18].

Internal logic of these systems is based on the use of a number of constants (heart rate (HR), respiratory rate (RR), body temperature, consciousness, complaints, level of neuropsychic development, etc.) that determine the age group. In threat measurement systems, these are more specific indicators, the violation of which will indicate the degree of risk. Systems of preventive examinations mainly indicate cardinal complaints, significant anamnestic information, deviations in status, and a number of laboratory and instrumental data. By summing up the scores, a profile of pathologies is determined that require further specialized interpretation. The system provides high reliability of information and diagnostic support for children over 5 years of age. This is due not only to the possibility of assessing intellectual development, but also to the degree of adaptation of a child to the children's environment [19].

Many systems of digital criteria for assessing children's health can be built depending on the set goals. The most adequate means of description,

[1] 2020 The European Child and Adolescent Health Strategy 2015–2020 and the European Action Plan to Prevent Child Maltreatment 2015–2020. 20.08.2020. Meeting Report. Available at: https://whodc.mednet.ru/ru/component/attachments/download/119.html (accessed: 17.03.2024).

 ISSN 2221-2582

in our opinion, are the methods of fuzzy logic, close and understandable to medical logic. To use this approach, as is known, it is necessary to specify membership functions corresponding to the required pathology profiles describing the "children's space". The issues of constructing membership functions and digital methods for assessing "children's space" have a number of features, since each membership function characterizes the degree of expression of a certain diagnostic feature (symptom). From a formal point of view, if we have Vj numbers of features that are significant for the PF profile, then these features are formed by medical experts. In this case, the primary formula for certain entry of the corresponding profile looks like this: $PF_j = \otimes A_k$, $k \epsilon V_j$. The operation formula $\otimes$, is used, which allows to accumulate small contributions of individual operands. At the same time, unlike conventional addition, the additivity effect is manifested here to a limited extent, i.e. the result never exceeds 1. Such a simple approach allows us to construct various sets of digital criteria for the "children's space".

Fig. 1. Screen-shot of pathology profiles in a 5-year-old child

Рис. 1. Скриншот профилей патологии у ребенка 5 лет

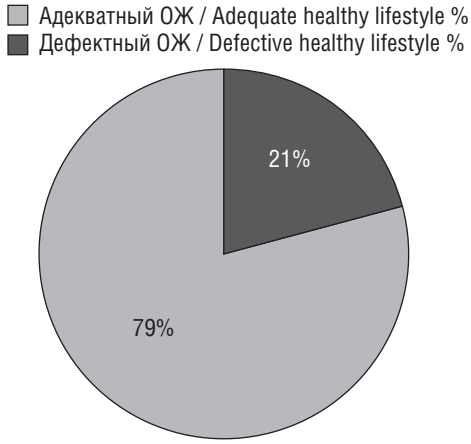

Fig. 2. Diagram of the ratio of adequate and defective educational life in a 5 year old child

Рис. 2. Диаграмма соотношения адекватного и дефектного образов жизни (ОЖ) у ребенка 5 лет

As an example, Figures 1 and 2 show examples of the conclusion of an effective remote screening system, demonstrating individual risks of chronic non-communicable diseases (CNCDs), the effectiveness of a healthy lifestyle (HLS) in the form of a screenshot and a pie chart.

In order to create a planar system for assessing threatening conditions (profiles), we can build rating scales based on the example of the Glasgow Coma Scale: 15–14 points — clear consciousness; 13–12 points — stupor; 9–11 points — sopor; 3–8 points — coma. We will assess the child's condition in a similar way: 14 points — satisfactory; 12 points — moderate; 9 points — severe; 8 and below — extremely severe.

Among functional parameters for a 5-year-old child, we highlight the temperature of 36.9 °C; pulse rate of 100 beats per minute, respiratory rate of 25 per minute; saturation of 95%, leukocytosis of 9.0×10^9 — 4 points; 10.0×109 — 6 points; 12×10^9 — 8 points; 14.0×109 — 10 points. Figure 3 shows a planimetric system of a threatening condition. Visualization allows for clear and objective monitoring of the condition of a sick child at any time of day and at any distance. Archiving the presented diagrams is the main evidentiary element of adequate management tactics.

It is much more difficult to form and create logical series in the comprehensive assessment of medical, social, environmental, psychological, national, spiritual and economic factors. We will conditionally express the gradation in points: 15 points — sufficient level, good; 10 points — questionable; 5 points — harmful, negative. The lines of research will be: hereditary background, negative factors of the perinatal period, the course of labour, family relationships, housing conditions, diseases of infancy, deviations in physical development, the dynamics of neuropsychic development, vaccination, the quality of preventive observation, attendance at kindergarten, the frequency of acute diseases, the performance of psychological tests, behaviour in a children's group, health group, the state of the environment. The results are shown in Figure 4.

The obtained results indicate serious, multifactorial negative influences on the development of a child's health. In this case, we can talk about the "narrowing of children's space." The constructed methodological chain has its own justification.

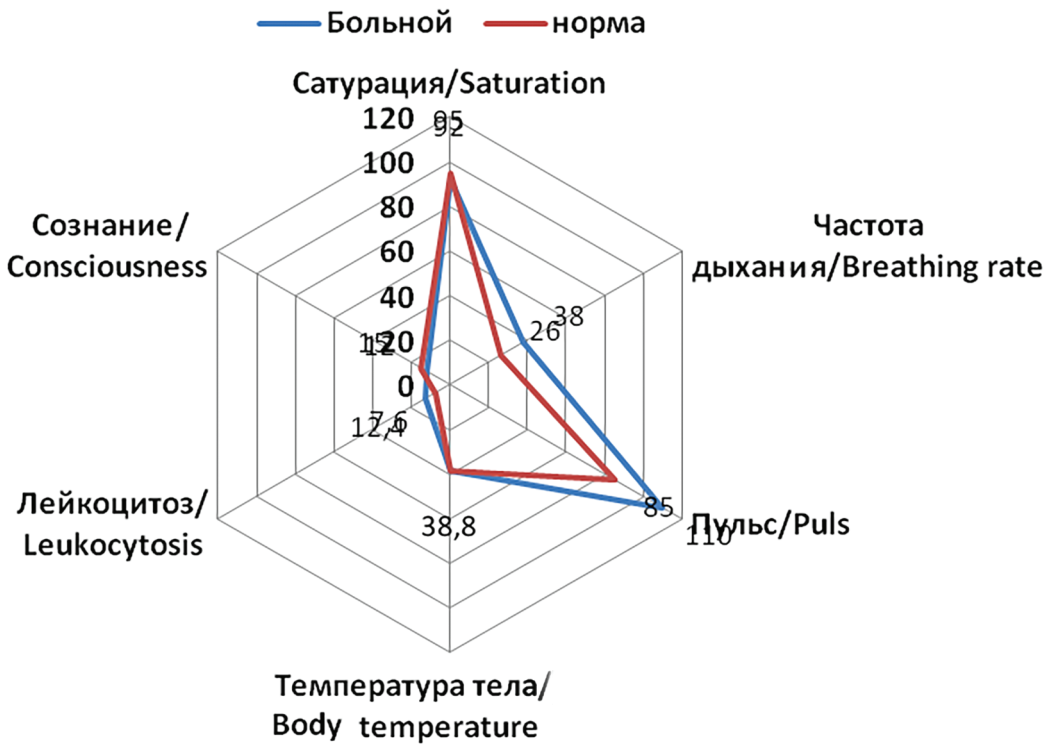

Fig. 3. Threat scheme of infectious-toxic shock

Рис. 3. Угрозометрическая схема инфекционно-токсического шока

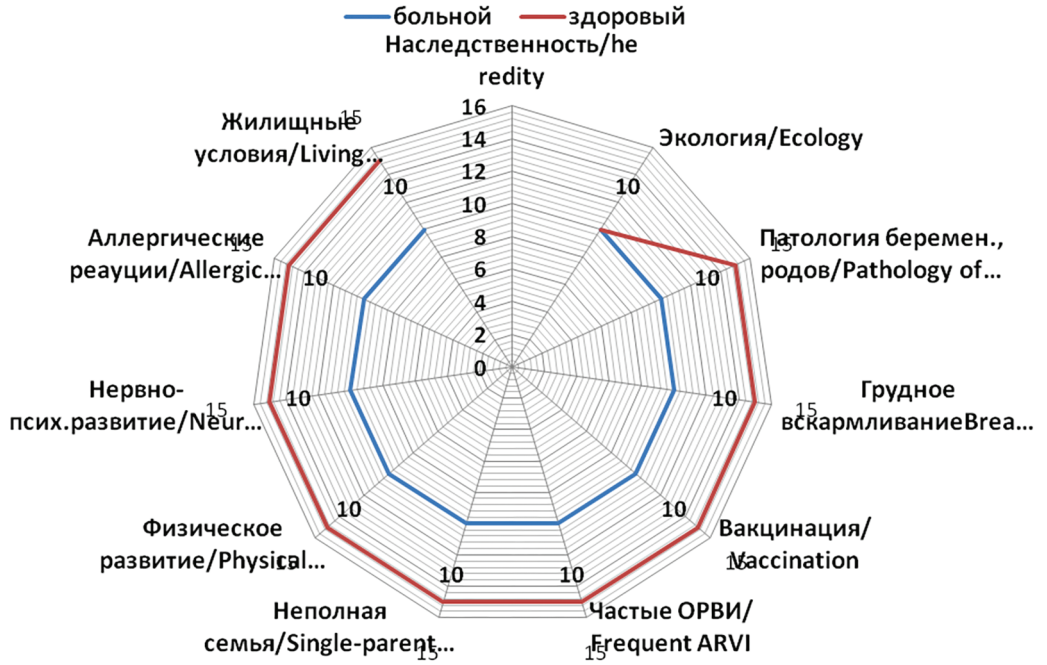

Fig. 4. Summary diagram of the health assessment ("children's space") of a 5 year old child

Рис. 4. Сводная диаграмма оценки здоровья («детского пространства») ребенка 5 лет

The presented material has already become firmly established in paediatric practice and is a tool for many scientific studies. This refers to the interaction of damaging factors and target organs, which can remain hidden for a long time. I.M. Vorontsov (2006) called this latent period the "ontogenetic interval". In this regard, it is necessary to ensure the earliest possible start of providing assistance, even at the resuscitation stage [20].

The main methodological approaches to organizing assistance are:

- the earliest possible start of providing assistance with an assessment of rehabilitation potential;
- implementation of inclusion and rehabilitation measures in full accordance with the level of biological maturity of a child;
- continuity between stages;
- development and implementation of an automated system for monitoring patients participating in the follow-up program with an assessment of the prognosis and effectiveness of the measures taken;
- three-stage nature of assistance with allocation of a follow-up centre (activities in intensive care unit, then neonatal pathology unit and follow-up unit);
- family-centred approach, involvement of relatives in rehabilitation process and creation of accessible psychological environment for the child's relatives;
- interdisciplinary team approach and professional training of medical and teaching staff for long-term work with the family.

DISCUSSION

Considering the methodology as a multi-level system, at the first philosophical level we substantiated the concept of "children's space", based on the interaction of external and internal factors with the child's body. At the second, most general level of the methodology, the fundamental factors of influence embedded in the comparative characteristics of the healthy child standard and a specific patient were identified (Fig. 4). Next, the method of visualization of priority factors was selected (third level). The fourth level determined the preparation of a conclusion on the conducted study, and the fifth (technological) confirmed the possibility of using this method in paediatrics [21, 22].

Thus, the introduction of digital technologies in paediatrics significantly expands our capabilities for implementing preventive measures and creates a program of action for parents and paediatricians for both healthy and sick children [23, 24].

In assessing the results of the study, it is necessary to dwell on some comprehensive definitions of modern problems related to childhood [16, 25]. The collection, published in 1996, characterizes the period of reforms as "a critical period of transition from ideological forms of modernization to "generally civilized" ones." Reference is made to "unprecedented situations requiring non-standard solutions", "decline in the educational level of the majority of children", and "the criminalization of the children's environment". Problems of demography, health, family relations, accessibility of the social and cultural environment, etc. have become sharply more acute. How could one comprehensively characterize the numerous factors that determine children's development? In our opinion, the term "children's space" has allowed us to incorporate the maximum number of dominant factors that influence children's health. We do not claim priority in terminology, but we consider it appropriate to use the term in the context of a comprehensive assessment. At the same time, the change in assessment can range from "narrowing" to "expanding" and "age-appropriate" children's space. We are not discussing the issue of controversy regarding the term, but are raising the question of a comprehensive assessment of the maximum number of factors that determine health of the child population. However, when a difficult situation was noted, the approach to assessing children's health remained traditional [26, 27]. Moreover, the introduction by S.M. Grombach of four criteria for determining a health group has now resulted in the presence or absence of chronic diseases.

When using digital technologies and evaluating graphic images, the terms must be clear and reflect the relationship between the reference and actual area of the "children's space". As with any value, in paediatrics within an age group there may be fluctuations, which can be assessed in centiles, sigma deviations, etc. The main task, which in our opinion is solvable, is to approach the most complete and structured assessment of the development of child's health, its monitoring and correction. We would like to believe that the V International Practical "Infoforum" for teachers will consider new approaches to the comprehensive assessment of children's health not only in medical but also in pedagogical terms [28].

CONCLUSION

The presented material does not claim to be a complete work, but shows the possibility of using digital technologies in attempts to comprehensively assess health of children for the purpose of monitoring and timely correction. The results obtained from preventive examinations conducted in accordance with the order of the Ministry of Health of the Russian Federation N 514n dated 10.08.2017 do not provide a complete picture in assessing pathogenic factors. Parents and health workers do not receive specific information about cause-and-effect relationships, which, in our opinion, limits the ability of children's medical and educational institutions and legal representatives to carry out both prescribed treatment and preventive measures and to monitor the health status.

Similarly, when assessing the "children's space" using a multi-stage method in rehabilitation, a patient's trajectory (routing) is formed in accordance with the order of the Ministry of Health of the Russian Federation dated November 23, 2019 N 878n "On approval of the Procedure for organizing medical rehabilitation of children".

ADDITIONAL INFORMATION

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

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

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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ISSN 2221-2582

UDC 616-07-08-053.4/.5+612.398.139+615.874.2+613.24
DOI: 10.56871/CmN-W.2024.90.64.003

PROTEIN-ENERGY INSUFFICIENCY IN ADOLESCENTS. FEATURES OF THE CURRENT (LECTURE)

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For citation: Podorova LA, Trapeznikova AYu. Protein-energy insufficiency in adolescents. features of the current (lecture). Children's Medicine of the North-West. 2024;12(3):18–26. DOI: https://doi.org/10.56871/CmN-W.2024.90.64.003

Received: 04.06.2024 **Revised: 18.07.2024** **Accepted: 10.09.2024**

Abstract. Protein-energy undernutrition is a global medical problem. The most vulnerable categories of the population are children and the elderly. According to World Health Organization, more than 17% of children under 5 years old suffer from various degrees of protein-energy undernutrition. It has been established that 25% of the Russian population experience nutritional deficiency, and 85% have various manifestations of hypovitaminosis. The widespread of nutritional and energy malnutrition is primarily due to socio-economic factors. The pathology is characteristic of residents of low-income countries who cannot afford food sufficient in calories and vitamin content. Adolescents represent a special group of the population, since at this age there is a formation of personality in society, the desire to achieve ideals of appearance and comply with modern fashion trends. It is they who, in pursuit of ideal figure parameters imposed by the media, are often victims of such advertising. In case of nutritional insufficiency, all organs and systems are involved in the pathological process. The degree of impairment depends on the duration and severity of malnutrition. With a slight lack of calories, the breakdown of glycogen in the liver is observed, due to which the body receives a sufficient amount of energy. There is a mobilization of fat reserves, an increase in the level of amino acids in the blood. Doctors of all specialties face manifestations of protein-energy deficiency, but a pediatrician is most often involved in identifying the initial forms of pathology. For diagnostics, it is very important to collect information about the nature of a person's nutrition, material and living conditions. This lecture highlights the basic concepts, diagnosis and treatment of this pathology.

Keywords: *adolescents, protein-energy undernutrition, diet therapy*

БЕЛКОВО-ЭНЕРГЕТИЧЕСКАЯ НЕДОСТАТОЧНОСТЬ У ПОДРОСТКОВ. ОСОБЕННОСТИ ТЕЧЕНИЯ (ЛЕКЦИЯ)

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Для цитирования: Подорова Л.А., Трапезникова А.Ю. Белково-энергетическая недостаточность у подростков. Особенности течения (лекция) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 18–26. DOI: https://doi.org/10.56871/CmN-W.2024.90.64.003

Поступила: 04.06.2024 **Одобрена: 18.07.2024** **Принята к печати: 10.09.2024**

Резюме. Белково-энергетическая недостаточность (БЭН) — глобальная медицинская проблема. Самые незащищенные категории населения — дети и пожилые люди. По данным Всемирной организации здравоохранения, более 17% детей младше 5 лет страдают от различных степеней БЭН. Установлено, что 25% населения России испытывают нутритивный дефицит, а у 85% выявлены различные проявления гиповитаминозов. Широкое распространение нутритивной и энергетической неполноценности питания обусловлено в первую очередь социально-экономическими факторами. Патология характерна для жителей стран с низким уровнем дохода, которые не могут позволить себе достаточную по калорийности и витаминному

содержанию пищу. Подростки представляют особую группу населения, поскольку в этом возрасте происходит становление личности в социуме, стремление достичь идеалов внешности и соответствовать современным тенденциям моды. Именно они в погоне за идеальными параметрами фигуры, навязываемыми средствами массовой информации, зачастую являются жертвами такой рекламы. При нутритивной недостаточности в патологический процесс вовлекаются все органы и системы. Степень нарушений зависит от длительности и тяжести недоедания. При небольшом недостатке калорий наблюдается распад гликогена в печени, за счет чего организм получает достаточное количество энергии. Происходит мобилизация жировых запасов, повышение уровня аминокислот в крови. С проявлениями БЭН сталкиваются врачи всех специальностей, но выявлением начальных форм патологии чаще всего занимается врач-педиатр. Для диагностики очень важно собрать сведения о характере питания человека, материально-бытовых условиях. В данной лекции освещены основные понятия, диагностика и лечение данной патологии.

Ключевые слова: *подростки, белково-энергетическая недостаточность, диетотерапия*

INTRODUCTION

Protection of health of the younger generation is the most important task of the state, because the basis of the adult's health is laid in childhood. Accelerated physical development (acceleration) was replaced by its slowdown (retardation). Over the past 30 years, a decrease in almost all somatometric indicators has been recorded. The patterns of physical development of modern children include gracilization of physique and underweight in 13–14% of children (in some regions this figure reaches 25%) [1]. Of particular concern is the disruption of physical development in adolescents, in particular an increase in the number of children with low weight and growth retardation [2], some of whom are on the verge of developing protein-energy undernutrition (PEU).

Protein-energy undernutrition — is a pathological condition characterized by the development of symptoms of proteins, energy, other macro- and micronutrients deficiency as a result of their relative or absolute deficiency. Such condition develops because of partial or complete starvation [3].

PEU can be primary or secondary depending on the reason of its development. Primary PEU develops on the background of insufficient food intake. As a rule, in patients with primary PEU, the diet is dominated by proteins of plant origin, which has low biological value. Secondary PEU develops on the basis of acute and chronic diseases: liver (hepatitis, cirrhosis), bowel (inflammatory bowel disease (IBD), celiac disease), pancreas (pancreatitis), infectious diseases. There is three degrees of PEU depending on percentage of weight loss.

- I — mild PEU (body mass deficiency is 10–20%);
- II — moderate PEU (body mass deficiency is 21–30%);
- III — severe PEU (body mass deficiency is 31% or more).

In the case of a sharp decrease in weight because of a chronic disease and, as a consequence, a change in the body composition, PEU is defined as cachexia.

The classification of cachexia is as follows:

- alimentary marasmus is a severe nutritional disorder caused by the depletion of somatic protein (mainly peripheral protein of muscle tissue);
- kwashiorkor is a severe nutritional disorder caused by the depletion of visceral protein (proteins of serum and internal organs);
- mixed form — marasmic kwashiorkor.

Nowadays, several mechanisms and nosological forms of this pathology are distinguished:

1) insufficient food intake: unbalanced nutrition for age, eating disorders, mental illness (anorexia, bulimia), gastrointestinal diseases: gastroesophageal reflux disease (GERD), chronic gastroduodenitis, peptic ulcer;
2) digestion and/or absorption disorders: intestinal enzyme deficiencies (disaccharidase deficiency), celiac disease, cystic fibrosis, Crohn's disease, ulcerative colitis;
3) accelerated catabolism: endocrinopathies (diabetes mellitus, hyperthyroidism), intestinal infections: viral infections, parasitic infections (helminthiasis, giardiasis);
4) increased need for nutrients: period of active growth during puberty, active physical activity, stress.

FEATURES OF COMPLAINTS AND PHYSICAL EXAMINATION OF ADOLESCENTS WITH PROTEIN-ENERGY UNDERNUTRITION

Diagnosis of PEU is often difficult due to the fact that this pathology does not have patho-

 ISSN 2221-2582

gnomonic symptoms and is accompanied by an abundance of non-specific complaints from various systems and organs. The main reasons for visiting a doctor are complaints of peeling skin, depigmentation, the appearance of ecchymosis, slow wound healing, hair thinning and hair loss, koilonychia, delamination and brittleness of nails. When examining mucous membranes, attention is paid to the development of cheilosis, glossitis, ulcers and cracks in the tongue, recurrent stomatitis, dry conjunctiva and cornea. When examining the musculoskeletal system, recurrent caries, muscle wasting and muscle pain are diagnosed. Patients report frequent infectious diseases associated with a decrease in body's immunobiological reactivity. Damage to the nervous system and development of emotional lability, decreased tolerance to physical activity, dizziness, headaches, and sleep disorders are possible to be presented in such patients. Impaired twilight vision, bleeding gums, and the development of anaemia indicate the development of polyhypovitaminosis. It is worth noting that the main complaint may be a noticeable decrease in weight or its indirect signs (change in clothing size, belt size), insufficient weight gain, and the presence of oedema.

Parents should pay attention to the appearance of "red flags": sudden changes in pace and volume of food intake, frequent trips to the toilet immediately after eating, extreme preoccupation with body shape and size, distorted body image, obsessive exercise, abuse of laxatives and/or diuretics.

Refeeding syndrome is a complex of metabolic disorders that occurs when refeeding in patients with initial nutritional deficiency. The clinical picture is dominated by multiple organ failure, arrhythmia, cerebral oedema, polyneuropathy, and DIC syndrome [4].

METHODS OF DIAGNOSTICS OF PROTEIN-ENERGY UNDERNUTRITION

Methods of diagnostics of PEU can be divided into few groups:

1) method based on a clinical picture and anamnesis;
2) laboratory diagnostics;
3) instrumental examination;
4) anthropometric measurement;
5) complex assessment methods.

The method based on a clinical picture and anamnesis includes collecting complaints and assessing the dynamics of weight gain. This method also includes an assessment of actual nutrition, which includes many methods, the optimal ones being: the daily nutrition reproduction method, the method of food intake analysis and the method of directly recording the food intake.

The daily food reproduction method, or questionnaire-survey method, is based on an assessment of the actual food products consumed over the past day. The obtained data are used to conclude about the composition of these products, as well as to calculate the nutritional and energy value of the diet, the balance of its composition and its compliance with needs of the adolescent's body. A major drawback of this method is a short observation period, which can lead to false conclusions about the adolescent's diet. Therefore, it is recommended to use this method for several days.

The method of analyzing the frequency of food intake involves assessing the frequency of consumption of specific foods over a given period of time. This allows us to identify the correlation between the eating or exclusion of certain foods in the diet and appearance of clinical signs of the disease. Also, this allows to diagnose a possible development of an eating disorder caused by avoidance or limitation of the consumption of specific foods.

The method of directly recording the food intake basis on weighing food before eating it, weighing its remains after eating it, and counting the amount of eaten food. This method is not suitable for a patient with a suspected or diagnosed eating disorder, as it may worsen the adolescent's condition.

Based on the analysis of the actual nutrition of children, the correspondence of energy value of the diet to the body's energy expenditure, the content and ratio of animal and plant proteins, the ratio of proteins, fats and carbohydrates in the diet and their correspondence to body's needs are assessed.

Laboratory diagnostic methods are necessary to identify metabolic disorders and deficiency states [5]. Blood test is not specific in the diagnosis of PEU. It allows to identify the presence of iron deficiency states (haemoglobin level, erythrocytes, RDW, MCH, MCHC, MCV), as well as changes in the leukocyte formula and absolute leukocyte count in presence of infectious diseases.

The more specific test is proteinogram. Total protein content as a summary indicator depends on a large number of factors and is a low-sensi-

tivity indicator. It may give false negative results when fraction of globulin increased and there is a dehydration. Albumin is a marker of the visceral protein pool. About 40% of albumin circulates in the vascular bed, and the majority is found in the interstitial fluid. However, the half-life of albumin is 18–20 days, and therefore it may reflect the severity of the disease rather than undernutrition in acute disorders. Dehydration, renal failure, and infusion of albumin preparations may lead to an increase in albumin concentration. A decrease in albumin level is observed in a number of oncological diseases, oedema, and liver failure. Although albumin has a number of limitations as a marker of nutritional status, its low concentration correlates with the severity of PEU, especially in chronic undernutrition, allowing it to remain the main laboratory indicator for assessing nutritional status.

For a more accurate diagnosis of malnutrition, proteins with shorter half-lives, such as prealbumin (transthyretin) and transferrin, which have half-lives of 1–2 and 7 days, respectively, can be used. Prealbumin and transferrin undergo the same distribution as albumin but may be a better and more sensitive indicator of nutritional status. Prealbumin reliably reflects malnutrition when there are no signs of inflammation and may be a marker of the effectiveness of nutritional correction. To exclude the influence of inflammation on the prealbumin level, it is recommended to evaluate the ratio of C-reactive protein and prealbumin, the concentration of which correlates with the degree of inflammation. Transferrin is a representative of the β-globulin fraction involved in iron transport. A decrease in its concentration in serum allows for the detection of earlier changes in protein metabolism, while an increase is observed in iron deficiency states.

Creatinine is synthesized in muscle tissue by the breakdown of creatine phosphate. It is generally used to assess renal function, but its concentration also increases with muscle wasting, allowing creatinine levels to be used as a diagnostic marker for PEU. Another indicator of muscle wasting is 3-methylhistidine. As muscle tissue breaks down, its concentration in urine increases. Nitrogen balance assessment is used for timely diagnosis of catabolic stage of the pathological process, assessment of protein metabolism dynamics and prescription of an adequate diet.

Instrumental diagnostics involves the use of electrocardiography, echocardiography, ultra sound examination of abdominal organs, as well as endoscopic methods: fibrogastroduodenoscopy and colonoscopy with a biopsy of gastrointestinal mucosa [6]. These methods allow for differential diagnostics of etiological factors in the development of PEU.

Anthropometric measurement is a simple and accessible method for studying and diagnosing PEU. The following are used: measuring weight and length (in bedridden patients)/height, measuring body mass index (BMI), body weight-to-age ratio, body weight-to-height ratio, height-to-age ratio, and BMI-to-age ratio [7, 8].

BMI is recommended as a reliable indicator of nutritional status and is calculated using the formula: BMI=M (kg)/height^2 (m)

Степень БЭН / Degree of PEU	ИМТ, кг/м^2 / BMI, kg/m^2
БЭН I / I PEU	17–18, 4
БЭН II / II PEU	15–16,9
БЭН III / III PEU	меньше 15 / less than 15

There is a risk of obtaining false BMI data in the presence of oedema, which increases weight.

The mid-upper arm circumference of the non-working arm is also assessed: a decrease of 10–20% is considered a mild degree of malnutrition, 20–30% is considered moderate, and 30% or more is considered severe.

Also, the body composition is assessed. Total body mass (TBM) consists of lean, or fat-free mass (LM), which is an indicator of protein metabolism, and adipose tissue (AT), which reflects energy metabolism: TBM = LM + AT.

Body composition can be determined using bioimpedance measurement. Bioimpedance analysis is based on measuring the total electrical resistance (impedance) of the human body to alternating current. The method is also based on differences in the specific electrical resistance of biological tissues due to their different fluid and electrolyte content [9]. The electrical impedance of biological tissues has two components: active resistance, the substrate of which are cellular and extracellular fluids, and reactive resistance, the substrate of which are cellular membranes.

Complex assessment methods. Subjective Global Assessment (SGA) proposed in 1987 by A. Detsky et al., includes anamnesis data (weight loss dynamics, dietary changes, gastrointestinal

Table 1. Subjective Global Assessment (SGA) by A. Detsky

Таблица 1. Субъективная глобальная оценка (SGA) по A. Detsky

Категории SGA / Categories SGA	A	B	C
Прием пищи / Meals	Не изменены по сравнению с обычными / Not changed from usual	Снижен или жидкая диета / Reduced or liquid diet	Гипокалорийная жидкая диета или голод / Hypocaloric liquid diet or hunger
Потери веса (% к обычному) за последние полгода / Weight loss (% to normal) over the past six months	Нет потерь или менее 10%, но вес стабилен в течение последнего месяца / No loss or less than 10%, but weight is stable during the last month	Потери 5–10%, вес продолжает снижаться / Loss 5–10%, weight continues to decrease	Более 10%, особенно если потери веса происходят в течение последнего месяца / More than 10%, especially if weight loss occurs within the last month
Симптомы нарушения функций желудочно-кишечного тракта / Symptoms of gastrointestinal dysfunction	Отсутствуют или длятся менее двух недель / Absent or lasting less than two weeks	Ежедневно рвота и/или диарея / Daily vomiting and/or diarrhea	Симптомы, препятствующие приему пищи или нарушению всасывания, длительностью более двух недель / Symptoms of obstruction or malabsorption lasting longer than two weeks
Функциональные возможности / Functionality	Не изменены / Not changed	Снижение активности, слабость, переутомление / Decreased activity, weakness, overwork	Постельный режим, слабость, повышение температуры вследствие переутомления / Bed rest, weakness, fever due to overwork
Стрессорный фактор / Stressor	Нет системных эффектов первичного заболевания / No systemic effects of primary disease	Отдельные системные эффекты, такие как лихорадка / Selected systemic effects such as fever	Тяжелый стресс, острый колит, травма, септицемия / Severe stress, acute colitis, trauma, septicemia
Осмотр выраженности симптомов / Examination of the severity of symptoms: • потери подкожного жира / subcutaneous fat loss; • мышечная слабость / muscle weakness; • другие признаки / other signs	Не выражены / Not pronounced	Выражены / Pronounced	Ярко выражены / Strong pronounced
Питательная поддержка / Nutritional support	Не нужна / No need	Противоречивые мнения, дополнительная нутритивная поддержка 20–24 ккал/кг может быть успешной / Conflicting opinions, additional nutritional support of 20-24 kcal/kg can be successful	Обязательна / Mandatory

symptoms, functional capabilities — bed rest or normal physical activity), examination results (muscle and subcutaneous fat thickness, oedema and ascites) [10].

According to this scale, patients with normal nutritional status are assigned grade A, with moderate PEU — grade B, with severe PEU — grade C (Table 1).

Degree II of PEU is characterized by pronounced changes in all organs and systems. Decreased appetite, periodic vomiting, sleep disturbance. BMI is 15–16.9. The skin is pale, pale-gray, dry and flaky (signs of polyhypovitaminosis). Elasticity, tissue turgor and muscle tone are reduced. Hair is dull and brittle. There is decreased food tolerance. Such patients have concomitant somatic pathology (pneumonia, otitis, pyelonephritis), deficiency states.

Degree III PEU is characterized by anorexia, general lethargy, decreased interest in the environment. BMI is less than 15. Breathing is shallow, sometimes apnoea may be observed. Heart sounds are weakened, muffled, a tendency to bradycardia and arterial hypotension may be observed.

METHODS OF TREATMENT/CORRECTION OF PROTEIN-ENERGY UNDERNUTRITION

Therapy for PEU in adolescents includes several stages:

1) search for the etiological factor and treatment of the underlying disease, for example, psychotherapy for nervous anorexia; sanitation of chronic foci of infection; treatment of diseases of the gastrointestinal tract, biliary system; special therapeutic nutrition for metabolic disorders, etc.;
2) adequate diet therapy;
3) additional drug correction if necessary;
4) provision of psychosocial assistance.

Diet therapy is one of the main methods of correcting PEU. The diet, rational menu with easily digestible dishes, increased frequency of meals, and an increase in daily caloric intake by 10–20% are important. To conduct adequate diet therapy, it is necessary to establish the degree of body weight deficiency, determine the child's needs for essential nutrients and energy in accordance with the degree of malnutrition, calculate the actual nutrition for the teenager and correct the qualitative and quantitative composition of the diet taking into account the obtained data and functional capabilities of a patient.

Calculation of the content of essential nutrients in the daily diet [11]: proteins (g/day) = AEE (actual energy expenditure) 0.15/4, but not more than 2–2.5 g/kg; fats (g/kg) = AEE 0.3/9; carbohydrates (g/kg) = AEE 0.55/4.

For seriously ill patients, the most universal and acceptable calculation is the actual energy requirement using the formula: $AEE = BR \cdot AF \cdot DF \cdot TF \cdot BMD$, where AEE is the actual energy expenditure; BR is the basal metabolic rate (kcal/day); AF is the activity factor, DF is the damage factor, TF is the terminal factor; BMD is the body mass deficit.

The calculation of the basal metabolic rate for young men (10–18 years) is carried out using the formula $(17.5 \cdot \text{weight}) + 651$, for girls of the same age: $(12.2 - \text{weight}) + 746$.

There are basic correction factors:

- AF: bed rest — 1.1, hospital ward — 1.2, general — 1.3;
- TF: body temperature 38 °C — 1.1, 39 °C — 1.2, 40 °C — 1.3, 41 °C — 1.4;
- BMD: from 10 to 20% — 1.1, from 20 to 30% — 1.2, more than 30% — 1.3;
- DF: minor surgeries — 1.1, fracture — 1.2, major surgeries — 1.3, peritonitis — 1.4, sepsis — 1.5, multiple injuries — 1.6, traumatic brain injury — 1.7, burns — from 1.7 to 2.2 depending on the area of damage.

There is also a need to adjust the diet towards increasing the caloric content of dishes, which can be done in several ways: increase the volume of food consumed per day, which is often problematic due to the lack/decrease in appetite in a teenager. It is necessary to increase the caloric content of the diet due to products with a high content of protein (cottage cheese, cheese, meat, eggs) and fats, which is a difficult task due to the reduced capabilities of the gastrointestinal tract.

The optimal way to enhance nutrition remains the use of special products for nutritional support, which are characterized by a complete, balanced composition of proteins, fats, carbohydrates, vitamins, minerals and micronutrients. It also has a low risk of water-electrolyte overload, the ability to accurately dose the product, and minimizes the risks of developing gastrointestinal dysfunction. The tasks of nutritional support include: ensuring the body's energy and building needs, maintaining active protein mass, tissue function, especially the immune system, skeletal and respiratory muscles, restoring existing losses, correcting metabolic disorders, preventing and treating multiple organ failure.

The algorithm for carrying out nutritional support includes the following stages:

1) determining indications and contraindications for nutritional support;
2) assessing the patient's needs for nutrients;
3) choosing the method of carrying out nutritional support;
4) choosing the formula;
5) monitoring the effectiveness of the nutritional support being carried out.

There are several ways to provide nutritional support [12]:

- sipping is the independent oral intake of liquid nutrition through a tube or in small sips in order to maintain and correct nutritional status in accordance with the patient's current needs for energy, protein, vitamins, minerals and microelements [13];
- enteral tube feeding (through a nasogastric or nasointestinal tube);
- enteral nutrition through a stoma (percutaneous endoscopic, laparoscopic, laparotomic) if the disease lasts more than 6 weeks; the choice of access is determined by the patient's ability to eat independently and the absence of signs of dysphagia;
- parenteral nutrition (PN) is the administration of nutrients intravenously, passing the gastrointestinal tract, in order to maintain and correct nutritional status in accordance with the patient's current needs for energy, protein, vitamins, minerals and microelements;
- mixed nutrition.

When choosing a method of nutritional support, preference should be given to enteral nutrition, which promotes maximum preservation of the gastrointestinal tract, in particular preservation of intestinal functions, the structure of the small intestine, limitation of bacterial translocation and septic complications, and reduces the likelihood of developing multiple organ failure. It should be remembered that the choice of tube feeding may entail the development of a number of complications, such as damage to the tube itself (for example, its twisting), damage to the mucous membrane, aspiration of gastric contents, and the manifestation of signs of dyspepsia.

With parenteral administration, the necessary formulas are administered through a peripheral or central vein. Parenteral nutrition (PN) can be complete or partial. In case of complete PN, preparations that provide the body's energy and building needs (amino acid solutions, fat emulsions and carbohydrate solutions) are used. Partial PN is of an auxiliary nature, is used to solve problems of short-term nutritional support of the body, includes individual nutritional components.

In addition to nutritional support, the treatment of PEU requires drug correction, which includes the administration of enzyme preparations. The most optimal forms are microspherical and microencapsulated forms of pancreatin, vitamins to correct deficiency states (ascorbic acid, B vitamins, vitamins A, E, D, K), iron preparations, and probiotics.

PROGNOSIS

The development of PEU can lead to a number of consequences, including digestive disorders, delayed wound healing, muscle mass reduction, decreased resistance to infections, anaemia, lymphopenia and hypoproteinemia, oedema formation and impaired blood transport function [14, 15]. Timely recognition of the pathology and correct selection of therapy contribute to the complete restoration of all systems in the adolescent, which significantly improves the patient's quality 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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC [616.21-022.6-08-059-06-084-085+615.33]-053.2-056.54
DOI: 10.56871/CmN-W.2024.64.58.004

BACTERIAL LYSATE OM-85 IN THE PREVENTION AND TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN FREQUENTLY AND LONG-TERM ILL CHILDREN (LITERATURE REVIEW)

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For citation: Kosenko IM. Bacterial lysate OM-85 in the prevention and treatment of acute respiratory infections in frequently and long-term ill children (literature review). Children's Medicine of the North-West. 2024;12(3):27–37. DOI: https://doi.org/ 10.56871/CmN-W.2024.64.58.004

Received: 10.06.2024 **Revised: 15.07.2024** **Accepted: 10.09.2024**

Abstract. Recurrent respiratory tract infections in frequently and long-term ill children are one of the most pressing and yet unresolved problems of modern pediatrics. Immunostimulants occupy a special place in the treatment of these infections. These medications are designed to neutralize existing disturbances in the immune response during the disease, which is especially important for patients who are often and long-term ill. The use of immunostimulants of microbial origin is one of the promising directions in increasing the effectiveness of the prevention and treatment of acute respiratory infections. Bacterial lysates are the most studied group among them. A review of available scientific publications is devoted to the analysis of the effectiveness and safety of the use of bacterial lysate OM-85 in complex therapy and prevention of acute respiratory tract infections in children. OM-85 is recognized as the most studied immunostimulating agent currently, the effectiveness and safety of which make it a valuable tool for optimizing the treatment of recurrent respiratory infections.

Keywords: *recurrent respiratory infections, frequently and long-term ill children, therapy, bacterial lysate OM-85*

БАКТЕРИАЛЬНЫЙ ЛИЗАТ ОМ-85 В ПРОФИЛАКТИКЕ И ЛЕЧЕНИИ ОСТРЫХ РЕСПИРАТОРНЫХ ИНФЕКЦИЙ У ЧАСТО И ДЛИТЕЛЬНО БОЛЕЮЩИХ ДЕТЕЙ (ОБЗОР ЛИТЕРАТУРЫ)

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Для цитирования: Косенко И.М. Бактериальный лизат ОМ-85 в профилактике и лечении острых респираторных инфекций у часто и длительно болеющих детей (обзор литературы) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 27–37.
DOI: https://doi.org/10.56871/CmN-W.2024.64.58.004

Поступила: 10.06.2024 **Одобрена: 15.07.2024** **Принята к печати: 10.09.2024**

Резюме. Рецидивирующие инфекции дыхательных путей у часто и длительно болеющих детей — одна из наиболее актуальных и пока не решенных проблем современной педиатрии. Особое место в терапии этих инфекций занимают иммуностимуляторы. Эти лекарственные препараты призваны нивелировать имеющиеся нарушения иммунного ответа при заболевании, что особенно актуально для часто и длительно болеющих пациентов. Одним из перспективных направлений в повышении эффективности профилактики и терапии острых респираторных инфекций является применение иммуностимуляторов микробного происхождения. Среди них наиболее изученная группа — бактериальные лизаты. Обзор имеющихся научных публикаций посвящен анализу эффективности и безопасности применения бактериального лизата ОМ-85 в комплексной терапии и профилактике острых инфекций дыхательных путей у детей. ОМ-85 признан

наиболее изученным в настоящее время иммуностимулирующим средством, эффективность и безопасность которого делают его ценным инструментом для оптимизации лечения рецидивирующих респираторных инфекций.

Ключевые слова: *рецидивирующие респираторные инфекции, часто и длительно болеющие дети, терапия, бактериальный лизат ОМ-85*

The majority of cases of acute respiratory tract infections (ARTI) in childhood are mild and uncomplicated. At the same time, severe disease and serious complications may develop, especially in patients with an unfavourable premorbid background (chronic lung and heart diseases, immunodeficiency, diabetes mellitus, and a number of other conditions) [1]. A special group is children with recurrent ARTI are those in whom the frequency and duration of respiratory infections are increased. Frequently and long-term ill children (FIC) are one of the most pressing and still unresolved problems of modern paediatrics, which has grown into a socially significant problem that worsens the psychological status of the child, reduces the general health of children and leads to "chronic sick leaves" [2]. In 40% of cases, by the age of 7–8 years, chronic pathology develops in FIC, and the risk of chronicity is directly proportional to the increase in frequency of episodes of acute respiratory infections (ARI) during the year [3].

The immune system of the FIC is in a state of extreme tension of immune response processes with impaired intercellular cooperation and insufficient reserve capacity. The result of a long-term, massive antigen impact on child's body and a high-risk factor for development of both local (addition of a bacterial infection) and general (development of immune pathology) complications are pronounced polymorphic changes in the form of combined (96.5%) and isolated (3.5%) defects of T-cell, humoral immunity, and neutrophil granulocyte system, as well as impaired ability of leukocytes to produce interferons [4]. In addition to severe immune disorders, a huge number of selective immunodeficiencies of a transient or permanent nature have been described [5, 6]. Clinical and immunological analysis allows us to state that the identified changes in immune system contribute to frequent recurrence of acute respiratory infections episodes and occurrence of complications [4].

In recent decades, the incidence of allergic diseases has been steadily increasing, including those affecting respiratory tract, which are often associated with recurrent nature of respiratory infections. Symptoms of respiratory atopy can either mimic the symptoms of respiratory infection or cause chronic respiratory tract inflammation and immunodeficiency, which causes frequent infections in children [7, 8].

The recurrent course of respiratory diseases in children is in the vast majority of cases associated with persistent infection [9]. A feature of the modern course of infectious pathology in children is a frequent combination of etiological factors, including viruses, bacteria, fungi and parasitic pathogens. Many infectious agents have the ability to long-term active persistence. These are representatives of the *Herpesviridae* family, "atypical" pathogens from the *Chlamydiaceae* and *Mycoplasmataceae* families [3, 10], and the bacterial flora of the upper respiratory tract [11–13]. The most frequently detected pathogens of persistent infections are representatives of the *Herpesviridae* family (herpes virus type 6, Epstein–Barr virus and cytomegalovirus), beta-haemolytic streptococcus group A, *Staphylococcus aureus* [9]. Moreover, herpes viruses are capable of causing significant disturbances in the immune status of macroorganism, thereby forming a vicious circle: chronic active herpesvirus infection — secondary immunodeficiency, against the background of which frequent acute respiratory tract infections are observed [10–12], and recurrent course of bacterial and parasitic diseases [6, 14, 15].

Without adequate treatment, respiratory infections often take a complicated or chronic course; a mild runny nose can result in severe pneumonia or sinusitis. Acute respiratory infections can also cause exacerbation of chronic diseases such as bronchial asthma, glomerulonephritis, heart diseases, etc. Timely therapy promotes faster recovery and prevents the development of complications. Of course, treatment should be comprehensive and built individually in each specific case [16]. Differentiated etiopathogenetic therapy and immunorehabilitation of FIC depending on the diagnosed persistent infection allows to achieve stable normalization of child`s condition and reduce frequency of antibiotic use [9].

Immunostimulants occupy a special place in the therapy of AID. These drugs are designed to

neutralize existing immune response disorders during the disease, which is especially important for frequently and long-term ill patients. It is assumed that use of drugs in this group will contribute to a more rapid relief of symptoms of respiratory infection, reduce the risk of complications and, accordingly, reduce the need for antibacterial therapy as well [17–19].

Based on the results of the immune status study, targeted selection of adequate immunocorrective therapy is not feasible. At the same time, the effects on the immune system are not indifferent to the body. Immunostimulants have multifaceted effects and are capable of causing unpredictable changes in body with minor effects, changing the balance in the immune system. At the same time, a deficiency or excess of one of the links of the immune system can lead to a violation of the correct response of the immune system. Therefore, it is necessary to use immunotropic drugs, assessing their need in each specific case and prescribing them not instead of, but together with basic therapy. It is necessary to remember that the effect of immunostimulants is of a triggering nature, and the response of the immune system is prolonged in time. The effectiveness of drugs can be judged no earlier than after 1–2 months [20].

Immunocorrective therapy for prevention and complex treatment of acute respiratory infections is indicated for patients [19]:

- with frequent acute and/or recurrent respiratory infections;
- living in ecologically unfavourable conditions and constantly exposed to negative environmental factors;
- with chronic respiratory diseases (chronic tonsillitis, bronchial asthma, rhinosinusitis, etc.);
- who have had a severe respiratory infection;
- from the risk group for development of recurrent respiratory diseases.

Currently, about 100 drugs are available in Russia that, according to the anatomical and therapeutic chemical classification, are classified as immunostimulants; many are intended for treatment and prevention of acute respiratory infections. However, a significant portion of these drugs do not have sufficient evidence base and therefore cannot be recommended for widespread use in respiratory infections in children [17–19].

One of the promising areas in increasing the effectiveness of immunotherapy and immunoprophylaxis of acute respiratory diseases is use of immunostimulants of microbial origin [17]. Among them, the most studied group is bacterial lysates, primarily OM-85.

Bacterial lysates contain components of microbial cells obtained by dissolving (lysing) bacteria — potential pathogens that have lost their viability. They retain the ability to stimulate immunity (innate and adaptive), but are not capable of causing infection (disease) [17, 19]. The production of bacterial lysates begins with fermentation, which ensures growth of the strain. Each bacterial strain is grown separately and inactivated at high temperatures. Destruction (lysis) of the bacterial cell walls is a key stage that allows obtaining different types of bacterial lysates. There are two methods of lysis of bacterial cell walls — mechanical and chemical. Mechanical lysis is carried out by mechanically destroying the cell wall (e.g., using high pressure, ultrasound, crushing the frozen mass, etc.), while chemical lysis is carried out using a chemical substance. After mass cultivation of reference bacterial strains, antigens are obtained either by mechanical or chemical lysis and lyophilization. Currently, there is no convincing data confirming that one or another lysis method (chemical or mechanical) provides an advantage in efficiency [17, 21]. Some authors claim that mechanical destruction may be a better alternative to chemical lysis due to the preservation of antigens. However, no studies have been conducted comparing the biological effects of polyvalent bacterial lysates prepared from the same bacterial cultures but using mechanical or chemical lysis procedures [21]. At the same time, OM-85 obtained by chemical lysis has a more extensive evidence base of efficacy and safety compared to bacterial lysate obtained by mechanical lysis [19].

Bacterial lysate OM-85 in capsule form contains lyophilisate of components of 21 strains of 8 different types of bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, Moraxella catarrhalis*) in the amount of 3.5 mg (form for children aged 6 months to 12 years) or 7 mg (form for children aged 12 years and adults). According to the instructions for medical use, this drug can be used as part of complex therapy for ARTIs and the prevention of recurrent respiratory tract infections [19, 22].

The effect of bacterial lysate OM-85 on immunological parameters has been well studied in numerous laboratory and clinical studies [18, 19, 23]. OM-85 is a systemically acting drug that enhances the mucosal immune response to both viral and bacterial infections in the respiratory tract by increa-

sing the efficiency of innate and adaptive immunity mechanisms. After oral administration of the drug, its capsule dissolves in stomach, releasing active components — bacterial lysates that pass through the intestinal mucosa into Peyer's patches, resulting in selective activation of dendritic cells, T- and B-lymphocytes, and the release of cytokines. Activated immune cells migrate throughout the body, mainly through the lymphatic system, especially to MALT (mucosal-associated lymphoid tissue) of the respiratory tract. The cellular and molecular mechanisms of OM-85 pharmacological action have been revealed (Table 1) [19, 24]. In particular, it has been established that under action of the drug, there is an increase in the level of interferons and a number of other cytokines in blood serum, which provides an antiviral effect, increases levels of immunoglobulins of classes G, M, A in blood serum, and of secretory immunoglobulin A, which provides an antibacterial effect.

Most studies of the bacterial lysate OM-85 are devoted to its prophylactic use [18, 19, 25, 26]. High prophylactic efficacy of this drug in children has been established in more than 50 clinical studies, the results of which were summarized in systematic reviews and meta-analyses [23, 24, 26–29]. Thus, in 2018, a systematic review with meta-analysis was published [23], which showed that the prophylactic use of the bacterial lysate OM-85 in children with recurrent ARTIs significantly reduces incidence of respiratory infections, reliably reduces the duration of diseases in general and their individual symptoms (fever, cough, wheezing in the lungs); significantly reduces the need for antibacterial drugs.

A number of clinical studies have also been conducted on the use of OM-85 bacterial lysate as part of combination therapy in the acute period of ARDI. Most of the studies were conducted in paediatric patients. In 10 controlled studies, which included a total of about 800 children (patients in the main group received OM-85 bacterial lysate as part of combination therapy, patients in the control group received standard treatment without an immunostimulant), there were differences in design and patient population (age and diseases), but the results obtained are largely the same. In particular, all studies noted a more rapid relief of ARTI symptoms in the main group [29–39]. Several studies also found that the use of an immunostimulant leads to a decrease of antibacterial therapy prescription [33, 34, 37, 38, 40].

In addition to clinical data, most studies analyzed the effect of OM-85 bacterial lysate on immune response parameters. It was found that patients in the main group had a reliable increase in the level of immunoglobulins (primarily IgA and IgG) compared to patients of the control group [30, 32–34, 36, 37, 39, 40]. Some studies showed a positive effect of the drug

Table 1. Characteristics and proposed mechanisms of action of OM-85 [19, adapted from 24]

Таблица 1. Характеристики и предполагаемые механизмы действия OM-85 [19, адаптировано из 24]

Антиген-презентирующие клетки / Antigen presenting cells	Врожденный иммунитет / Innate immunity	Адаптивный иммунитет / Adaptive immunity
• Созревание мезентериальных дендритных клеток (ДК) / Maturation of mesenteric dendritic cells (DCs) • Увеличение продукции цитокинов / Increased cytokine production • Стимуляция противоинфекционной защиты респираторного тракта / Stimulation of anti-infective defense of the respiratory tract	• Высвобождение антимикробных пептидов (β-дефензина и рецептора C1q-компонента комплемента) / Release of antimicrobial peptides (β-defensin and complement component C1q receptor) • Снижение экспрессии ICAM / Decreased expression of ICAM • Цитокиновая активация NK-клеток, моноцитов, фагоцитоза, нейтрофилов / Cytokine activation of NK cells, monocytes, phagocytosis, neutrophils • Активация макрофагов (ИЛ-1β, ИЛ-6, ФНОα) / Activation of macrophages (IL-1β, IL-6, TNFα). • Высвобождение антивирусных цитокинов (ИФНβ) / Release of antiviral cytokines (IFNβ)	• ДК-индуцированная активация Т-лимфоцитов / DC-induced T-lymphocyte activation • Увеличение уровней CD8+, ИЛ-6, ИЛ-10 (про В-клеточных цитокинов), сывороточных и секреторных IgA/IgG / Increased levels of CD8+, IL-6, IL-10 (pro-B-cell cytokines), serum and secretory IgA/IgG • Созревание В-клеток из спленоцитов / Maturation of B cells from splenocytes • Увеличение уровней ИФНγ и IgG2/анти-ИЛ-4 / Increased levels of IFNγ and IgG2/anti-IL-4 • Высвобождение антивирусных цитокинов (ИФНα/ИФНγ) / Release of antiviral cytokines (IFNα/IFNγ)

on other components of the immune system, in particular an increase in the level of interferons [35, 36, 40]. Three studies showed a decrease in the incidence of complications of acute respiratory infections (ARI) against the background of OM-85 use [35, 38–40].

In 7 of the 10 discussed studies, not only therapeutic but also prophylactic effect of OM-85 bacterial lysate was assessed. Patients in the main group, in addition to the course of treatment during the ARI period, received two prophylactic courses of the drug [30–35, 37, 40]. All these studies have shown a significant reduction in the number of recurrent respiratory infections when using the immunostimulant.

In addition, a large clinical study that included 587 children under 12 years of age with recurrent ARTIs deserves attention. It compared the frequency and duration of respiratory infections before and after taking the bacterial lysate OM-85. The drug was administered starting with the next episode of respiratory infection and continued for 10 days (then two more preventive courses were administered according to the standard scheme). Against the background of treatment with the bacterial lysate OM-85 (as part of complex therapy), the average time to improvement (from 6.77 to 3.76 days) and recovery (from 11.86 to 7.36 days) significantly decreased. Follow-up observation showed more than 7-fold reduction in the number of ARTI relapses and a 10-fold reduction in the frequency of antibacterial therapy [41].

Thus, the available scientific data demonstrate high efficiency of using the bacterial lysate OM-85 for therapeutic purposes in children with ARTI. Inclusion of the drug in the composition of complex therapy significantly increases efficiency of therapeutic measures, which allows us to recommend it not only for prevention, but also for treatment of respiratory infections in paediatric practice.

According to the opinion of experts of the All-Russian public organization "Paediatric Respiratory Society", based on the results of evidence-based clinical studies, the bacterial lysate OM-85 can be used in children in the following situations (Table 2) [19]:

- in the initial period of ARTI (as part of complex therapy) — in order to speed up recovery and reduce manifestations of the disease, as well as to prevent development of bacterial complications and, accordingly, reduce the need for antibacterial therapy;
- in complicated respiratory infections (as part of complex therapy, including in combination with antibacterial drugs) — in order to contain further disease progression, increase the effectiveness of antibacterial therapy and reduce the risk of antibiotic-resistant bacterial strains selection;
- during the convalescence period (as part of rehabilitation) — in order to more quickly restore the body, prevent recurrent course of ARTI and chronization of the disease;
- in recurrent ARTI — in order to prevent repeated respiratory infections and progression of chronic respiratory system diseases.

In addition, it is necessary to remember that severe and repeated viral respiratory tract infections, especially in early childhood, are associated with the risk of bronchial asthma developing. The conducted studies, including a meta-analysis and a systematic review [24, 42–46], showed that bacterial lysates are a promising additional tool to the current treatment of wheezing in preschool children and asthma in childhood, they can be considered as a safe and effective additional therapy for dyspnoea in preschool children and in children with recurrent exacerbations of asthma.

In the complex treatment of acute respiratory infections, OM-85 can be used in combination with other drugs, including antiviral and antibacterial ones [22].

To reduce the burden of recurrent respiratory infections, combined use of OM-85 and influenza vaccine was recognized as effective and safe, improving existing prevention strategies [47–49].

Experimental studies have shown that OM-85 *in vitro* reduces the binding of SARS-CoV-2 to bronchial epithelial cells, suppresses the expression of the ACE2 receptor, a key factor in the penetration of SARS-CoV-2 into bronchial cells. OM-85 can reduce binding of the SARS-CoV-2 S protein to epithelial cells by modifying host cell membrane proteins and specific glycosaminoglycans. Thus, OM-85 can be considered as an adjunct to COVID-19 therapy. The data obtained confirm the known antiviral effects of OM-85 on respiratory viruses (including SARS-CoV-2) [50, 51].

In Long-COVID infection, the use of OM-85 is recommended to stimulate mucosal immunity. Its use in the complex treatment of respiratory infection is aimed at reducing the risk of secondary bacterial infection and the need for antibiotics. OM-85 should be recommended as a prophylaxis for recurrent respiratory and secondary bacterial infections [52].

Available data suggest that OM-85 can effectively and safely reduce the risk of new infectious episodes in children with recurrent ARIs, and that repeated annual courses of lysate administration

 ISSN 2221-2582

Table 2. Clinical situations when the use of bacterial lysates is advisable [19]

Таблица 2. Клинические ситуации, когда прием бактериальных лизатов целесообразен [19]

Клиническая ситуация / Clinical situation		Цель назначения / Purpose of appointment
Острая респираторная инфекция (комплексное лечение) / Acute respiratory infection (complex treatment)	В начале заболевания / At the beginning of the disease	• ускорение процессов выздоровления / acceleration of healing processes; • предотвращение развития бактериальных осложнений / prevention of development of bacterial complications; • уменьшение клинических проявлений воспалительного процесса / reduction of clinical manifestations of the inflammatory process; • снижение потребности в антибиотикотерапии / reduction in the need for antibiotic therapy
	При прогрессировании заболевания (вместе с антибиотиками) / As the disease progresses (along with antibiotics)	• ускорение процессов выздоровления / acceleration of healing processes; • повышение эффективности антибактериальной терапии / increasing the effectiveness of antibacterial therapy; • снижение риска сохранения в организме антибиотикорезистентных штаммов бактерий / reducing the risk of antibiotic-resistant bacterial strains remaining in the body; • уменьшение клинических проявлений заболевания / reduction of clinical manifestations of the disease; • ограничение дальнейшей генерализации инфекции, профилактика хронического воспаления / limiting further generalization of infection, preventing chronic inflammation
Реабилитация / Rehabilitation		• ускорение репаративных процессов / acceleration of reparative processes; • профилактика рецидивов и хронизации заболевания / prevention of relapses and chronicity of the disease
Профилактика / Prevention		• стойкая защита слизистой оболочки дыхательных путей от патогенов / persistent protection of the respiratory mucosa from pathogens; • предотвращение повторных острых респираторных инфекций и снижение их тяжести / prevention of recurrent acute respiratory infections and reduction of their severity; • предотвращение обострений и прогрессирования хронических респираторных заболеваний / prevention of exacerbations and progression of chronic respiratory diseases

may be useful for maintaining protection, especially when recurrent ARIs are diagnosed in young children, for whom final maturation of the immune system probably requires a long time [48].

The OM-85 drug has a favourable safety profile, which supports the possibility of its long-term use. Over past 40 years, more than 61 million children have received OM-85 bacterial lysate. According to observations, the drug is well tolerated by children. A meta-analysis of 14 studies (n=1859) and a Cochrane analysis of 9 studies (n=852) showed no significant association between the use of OM-85 in children with recurrent respiratory tract infections and an increased incidence of adverse reactions compared to placebo. Adverse events in children with recurrent respiratory tract infections were reported in 33 of 53 studies included in the meta-analysis, and they did not affect treatment outcomes. In 85% of cases, non-serious adverse events were noted. There were 538 cases of hypersensitivity in children and adults, and 57% of them had skin lesions only [48, 49, 51, 53, 54].

However, the number of studies with a high level of evidence devoted to the therapeutic efficacy of OM-85 bacterial lysate is currently small. In order to form final conclusions about the efficacy of the drug and practical recommendations for its optimal use, it is advisable to conduct well-designed clinical trials with a high level of evidence on a sufficient number of patients, as well as to summarize the results of evidence-based clinical trials in systematic reviews and meta-analyses [40]. Despite this, OM-85 is recognized as the most studied of currently available immunostimulants, which efficacy and safety make it a valuable tool for optimizing treatment of recurrent respiratory infections in both adults and children [47].

The indication for the use of OM-85 is included in numerous clinical guidelines and consensus documents on recurrent respiratory tract infections in children [55–58]. Bacterial lysates are the only agents from the immunostimulant group that are included in the clinical guidelines of the Ministry of Health of the Russian Federation "Acute respiratory tract infection (ARTI)": "For children under 6 months, with recurrent infections of the ENT organs and respiratory tract, the use of other immunostimulants (systemic bacterial lysates) is recommended. The strength of the recommendation is A; the level of evidence is 1" [59].

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Competing interests. The author declares the absence of obvious and potential conflicts of interest related to the publication of this article.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Автор прочитал и одобрил финальную версию перед публикацией.

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

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

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ISSN 2221-2582

UDC 612.39+641/642+796+616-053.2
DOI: 10.56871/CmN-W.2024.47.40.005

CURRENT APPROACHES TO NUTRITION OF CHILDREN INVOLVED IN SPORTS (LITERATURE REVIEW)

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For citation: Bairova SV, Sakhno LV, Koltuntseva IV, Emelyanova AV, Kaprior EV. Current approaches to nutrition of children involved in sports (literature review). Children's Medicine of the North-West. 2024;12(3):38–48. DOI: https://doi.org/10.56871/CmN-W.2024.47.40.005

Received: 20.05.2024 **Revised: 27.07.2024** **Accepted: 10.09.2024**

Abstract. Proper nutrition for children involved in sports will help to correct the possible adverse effects of increased physical activity, achieve high performance and improve the health of young athletes. Knowledge about the rational nutrition of athletes should be available not only to doctors of sports dispensaries, but also to outpatient doctors, since a large number of children are engaged not only in sports schools, but also at additional education sites and do not always visit dispensaries. The article discusses the basic principles of rational nutrition of children involved in sports, adopted in the Russian Federation. Preparation of a balanced diet, taking into account the type of sport, the intensity of loads and the period of training activity; the use of adequate forms of nutrition, including specialized products, standards of basic nutrients, mineral and vitamin support and drinking regimen. Foreign approaches to nutrition of athletes' children are similar to domestic recommendations. Of interest is a new direction in nutrition using probiotic products to maintain the microbiome that affects the psychological state of an athlete, as well as measures of nutritional support for vegan children. The appointment of adequate nutrition for children involved in sports will allow them to achieve high results while maintaining their health.

Keywords: *nutrition, sports, children, dysmicroelementoses, dysmacroelementoses*

АКТУАЛЬНЫЕ ПОДХОДЫ К ПИТАНИЮ ДЕТЕЙ, ЗАНИМАЮЩИХСЯ СПОРТОМ (ЛИТЕРАТУРНЫЙ ОБЗОР)

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Для цитирования: Баирова С.В., Сахно Л.В., Колтунцева И.В., Емельянова А.В., Каприор Е.В. Актуальные подходы к питанию детей, занимающихся спортом (литературный обзор) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 38–48. DOI: https://doi.org/10.56871/CmN-W.2024.47.40.005

Поступила: 20.05.2024 **Одобрена: 27.07.2024** **Принята к печати: 10.09.2024**

Резюме. Правильное питание детей, занимающихся спортом, поможет скорректировать возможные неблагоприятные воздействия усиленных физических нагрузок, добиться высокой работоспособности и улучшить состояние здоровья юных спортсменов. Знания о рациональном питании спортсменов должны быть как у врачей спортивных диспансеров, так и у врачей амбулаторного звена, потому что большое число детей занимаются не только в спортивных школах, но и на площадках дополнительного образования и не всегда посещают диспансеры. В статье рассматриваются основные принципы рационального питания детей, занимающихся спортом, принятые в РФ. Составление сбалансированного рациона питания с учетом вида спорта, интенсивности нагрузок и периода тренировочной деятельности, использование адекватных форм питания,

в том числе специализированных продуктов, нормативы основных питательных веществ, минерально-витаминной поддержки и питьевого режима. Зарубежные подходы к питанию детей-спортсменов, схожи с отечественными рекомендациями. Представляют интерес новое направление в питании с использованием пробиотических продуктов для поддержания микробиома, влияющего на психологическое состояние спортсмена, а также меры нутритивной поддержки детей-веганов. Назначение адекватного питания детям, занимающимся спортом, позволит добиться высоких результатов при сохранении их здоровья.

Ключевые слова*: питание, спорт, дети, дисмикроэлементозы, дисмакроэлементозы*

INTRODUCTION

In recent years, the Russian Federation has paid considerable attention to the development of children's sport. Russia is implementing the federal project "Sport is the norm of life" (https://norma-sport.ru/) from January 2019 to the end of 2024. Its goals are to promote healthy lifestyles and rational nutrition, to improve conditions for physical education in Russia, primarily for the child population [1, 2]. The "Concept of development of children's and youth sports in the Russian Federation until 2030" was adopted in December 2021. Its aims are supporting and developing children's and youth sports as a priority area in the social policy of the state, which is of crucial importance for the future of the country, contributing to increasing the duration and improving the quality of life of Russian citizens, revealing the talent of each person, including persons with disabilities and persons with disabilities [3]. The measures taken have led to the fact that sports activities have become more widespread. About 23 million people aged from 3 to 18 years (85% of the total number of children and youth, according to 2019 data) are systematically engaged in physical culture and sports in the Russian Federation. According to the Ministry of Sport, in Russia 41% of children aged 6 to 15 years are engaged in specialized sports institutions [4]. Regular sports activities have a positive impact on the development and health of children, ensure full physical and intellectual development, and instill a culture of a healthy lifestyle. The positive influence of sports activities on psychological well-being and mental health of children has been proved [5]. All this creates strong prerequisites for comprehensive harmonious development of the younger generation [6].

At the same time, high physical and psychological activities against the background of active growth of a child can lead to unfavorable consequences for the health of a young athlete. Depending on the type of sport, the athlete's body is exposed to excessive or uneven impact of physical load, which can lead to disorders of various organs and systems. For example, hockey players have flat feet in the first place among the background conditions, and in 50% of cases fencers have pathology of the musculoskeletal system — posture disorders and scoliosis [7].

Athletes who specialize in one sport for a long time have higher injury rates. In addition, in individual sports there are significantly more injuries from overstrain than in team sports [8, 9].

Training activities of young athletes require the tension of metabolic processes, increased expenditure and demand for energy, vitamins and minerals. Therefore, the deficiency of macro- and microelements is observed in a significant number of young athletes. Deficiency of bioactive elements leads to homeostasis disturbance, which limits vital functions of the organism [10]. Individual peculiarities of indicators of chemical elements in the studied biological substrates in terms of calcium, iron, selenium, and magnesium have been revealed. The levels were different and depended on the type of sport. The levels of calcium and magnesium in saliva are reduced, and the iron content in hair is increased in fencers. Children involved in field hockey are characterized by higher values of zinc levels. The obtained data reflect the intensification of mineral metabolism under conditions of intensive physical exertion. Statistically significant interrelation of potassium and selenium indicators was proved when comparing the content of bioelements in hair and saliva. These results substantiate the necessity to single out young athletes into a risk group for the development of dysmacro- and microelementosis [11, 12]. One of the most common conditions is iron deficiency. All athletes are at risk of developing iron deficiency anemia due to increased iron requirements and impaired iron absorption due to hepcidin, the level of which increases against the background of intense physical exertion. Regular monitoring of blood iron profile and adequate correction in case of its violation are necessary for all young athletes [1].

Various hypovitaminoses are also quite often detected in most athletes and have a combined character. In a study to assess the provision of young athletes with vitamins E, A, C, B_2 and caro-

tene, conducted at the Scientific Center for Children's Health of the Russian Academy of Medical Sciences together with the Research Institute of Nutrition of the Russian Academy of Medical Sciences, it was shown that the deficiency of one vitamin (usually vitamin B_2 or carotene) in young swimmers was observed in 31% of cases. In 49% of children there was a deficiency of two vitamins simultaneously (most often B_2 and carotene). Combined deficiency of three vitamins (vitamin E, carotene and vitamins A or B_2) was experienced by 15% of children. At the same time, the level of vitamin C in more than half of athletes was determined at the upper limit of the norm (excessive supply), which was associated with the common practice of children taking a drink containing only one vitamin C in an amount 1.5–2 times higher than the recommended daily intake during training [14].

Nutrient deficiency in adolescent girls, especially in sports associated with the need to maintain a certain weight, can lead not only to deterioration of general health, performance, but also psychological state with the development of eating disorders. This knowledge is lacking in athletes, coaches and parents alike [15].

Due to the high risks of health disorders in young athletes, it is necessary to provide medical support for such children with periodic medical examinations [16] and development of individual recommendations based on the child's health status, primarily on rational nutrition. This knowledge should be possessed by a district pediatrician, since some children are not only involved in sports schools and do not always visit sports dispensaries.

FORMATION OF A PROPER DIET OF CHILD ATHLETES

Proper nutrition ensures a high level of performance, psychophysiological state and health of athletes. The nutrition of child athletes differs significantly from that of adults, since along with the need to ensure an effective training process, it is important to support the natural processes of growth and development of the child. The main approaches to nutrition of child athletes are considered in the methodological recommendations of the chief nutritionist of the Ministry of Health of the Russian Federation, academician of the Russian Academy of Sciences V.A. Tutelyan [17]. The main principles of rational nutrition of an athlete are: an individual approach, supplying the necessary amount of energy (respectively high spending); balanced nutrition taking into account the type of sport, intensity of loads and period of training activity; use of adequate forms of nutrition, including specialized products. It is necessary to prescribe a dietary regime, selecting the amount of proteins, fats, carbohydrates and mineral and vitamin support, drinking regimen and specialized food product if necessary depending on the age of the athlete, type of sport and training regimen [18].

Thus, during aerobic loads (weightlifting, power loads) it is necessary to increase protein in the diet. However, it should be remembered that the excess of protein over 2 g/kg per day is undesirable and does not lead to the strengthening of adaptive abilities of the body, and in some cases can lead to adverse effects — the impaired kidney function and negative calcium balance. The average norms of protein intake are 1.2–1.7 g/kg per day [19]. The ratio of proteins of animal and vegetable origin should be at least 60% and 40%, respectively. Foreign norms of protein requirements coincide with the Russian recommendations [20]. Modern nutritional standards indicate the ratio of proteins and fats 1:0.8–0.9 as the most favorable in the diets of young athletes. The main food sources of polyunsaturated fatty acids (PUFAs) of the omega-3 family are fish and seafood. Some vegetable oils are good sources of PUFAs — flaxseed oil, pumpkin oil, rapeseed oil. Their optimal share in the diet is 25–30% of the total amount of consumed fats. It is recommended to consume carbohydrates in the form of polysaccharides (starch) up to 65–70%, in the form of simple and easily digestible carbohydrates (sugar, fructose, glucose) about 25–30% and 5% in the form of dietary fiber.

Anaerobic exercise (cycling, skiing, swimming) increases total calorie intake, primarily due to carbohydrates (low glycemic index) and fats. In mixed aerobic-anaerobic exercise (playing sports), the diet approaches that of a healthy child with a slight decrease in fat and an increase in protein, depending on age and type of exercise. The optimal ratio of protein to fat is 1:0.8–0.9 [18].

Not only the diet, but also the mode of nutrition is important in the formation of health of young athletes. Optimal is considered 4–5 meals with intervals of 2.5–3.5 hours. Before the start of training after the main meal should be at least 1–1.5 hours for sports associated with prolonged physical exertion, and for speed and power sports

that interval should be at least 3 hours. An interval of no more than 1 hour after training is considered optimal. Distribution of caloric content of the daily ration during the day also takes into account the time and number of training sessions. The energy value of the first meal should not be not less than 10–15%, and the second is 20–25% of the total daily caloric content. The caloric value of lunch is 35%, afternoon snack is 5–10%, dinner is no more than 25% of the total daily caloric value of the diet. The last meal should be 1.5–2 hours before bedtime [21].

Calculation of daily energy expenditure should be carried out depending on the type of sport, period of training process, age and sex of athletes. Accordingly, the main diet is corrected in terms of calorie intake [22–24].

Compliance with the water regime is essential for maintaining homeostasis and high physical performance. Water is involved in the accumulation of glycogen in muscles. The daily need for free fluid varies from 1.5–2 to 5–6 liters and depends on the age, health, physical activity of the child, as well as the ambient temperature. It is advisable to use sports drinks containing carbohydrates and electrolytes. Drinks containing caffeine, guarana extract and other stimulants are prohibited for child athletes [25].

NUTRITION OF ATHLETES DURING THE COMPETITION PERIOD

Organization of rational construction of the training process and increase of its efficiency is possible only with a properly designed diet, corresponding to the energy expenditure of the athlete and including all essential components of nutrition. Special attention should be paid to nutrition in the period of competition. The organization of nutrition in the period of intense physical exertion provides for the use of products of increased biological value, for a directed effect on the metabolism in the body both before and after the competition period. The use of biologically active additives in the pre-competition, competition and recovery periods should be carried out in accordance with the type of sport and preferably with the addition of trace elements (magnesium, potassium, calcium, chromium, iron, zinc and selenium) [26]. Individual nutrition programs for young athletes in the pre-competition period are developed for different sports, such as judo as one of the energy-consuming martial arts, where there is a need for weight loss, which, given the characteristics of the child's body, requires a competent approach. Dietary restrictions in pre-competition weight loss should be limited to fats and sugars only. Starvation and complete avoidance of water intake is contraindicated. Reduction of food calories is possible by 25–30%, in rare cases up to 50% of the usual consumption. The start of weight loss should be determined in advance and planned at least two weeks before the upcoming important competitions [27].

Energy-intensive sports also include cyclic sports such as cycling, short track, rowing (academic rowing, canoeing), swimming, speed skating (multiathlon), skiing (cross-country skiing, biathlon, Nordic combined), track and field, modern pentathlon, triathlon. The load is performed with high tension and significant intensity in all of these disciplines. Accordingly, the ratio of the main nutrients in endurance athletes is shifted in favor of carbohydrates, which should cover the high needs for physical activity, depending on the stage of the training process and the amount of load. The use of high-fat diets to provide energy function is not justified, the fat content in the diet of athletes should be about 25% of the total caloric content of the diet. Protein content should not exceed 1.2–1.6 g / kg of weight. The consumption of sports drinks containing carbohydrates and electrolytes is mandatory. Furthermore, it is more preferable than drinking only water [28].

SPECIALTY FOODS, VITAMIN AND MINERAL SUPPLEMENTS

The use of specialized food products has a number of advantages: a given chemical composition (a small volume contains an adequate amount of balanced nutrients in an easily digestible form), increased nutritional and biological value and/or directed efficiency allow to compensate for high energy expenditures in a small volume. However, the list of specialized products for child athletes approved for use in the Russian Federation is extremely limited. Currently, there are no foreign-made products that have an official certificate of state registration [17]. There are very few domestic products of specialized nutrition, only two products are allowed for use in child athletes from 6 years of age and 11 years of age. Studies on the use of these products have shown that a group of athletes receiving these specialized foods had normalized nutritional status and body mass index, increased performance and functional reserves of the body, which was manifested by improved sports performance [29–31].

The need for minerals and vitamins in children engaged in sports is much higher, especially in potassium, magnesium, calcium, phosphorus, iron, vitamin A, E, D, which requires mandatory correction. Vitamins are almost do not synthesize independently in the body. In this regard, it is necessary to monitor their intake with food, and if necessary, to address the issue of additional intake of multivitamin preparations or fortified foods. Lack of vitamins in the diet negatively affects the general state of metabolism and performance of young athletes [32].

The recommendations of sports dietitians in Australia (SDA) indicate the mandatory need for correction of vitamin D, calcium and iron, while the SDA position is that the nutrient requirements should be met by the main products, rather than supplements [33].

CURRENT TRENDS IN THE NUTRITION OF YOUNG ATHLETES

The positions of foreign sports nutritionists regarding the nutrition of child athletes (Canada, America) are similar to the Russian recommendations on the main directions. Attention is paid to individual selection of vitamin and mineral supplements and specialized food products. The issues of nutritional correction of vegetarian athletes with a risk of low intake of protein, fat and micronutrients (iron, calcium, vitamin D, riboflavin, zinc and vitamin B_{12}) are considered. Vegan athletes have low levels of carnosine and creatine, which also need correction. Such children need the consultation of a sports dietitian. Domestic guidelines do not accept a vegan diet in professional sports, especially in children. Despite the availability of theoretical data, the results of practical research on the effect of vegan diet on athletes' health and performance are needed [34, 35].

Works on the study of microbiome and its significance on the functional capabilities of an athlete have appeared, recommendations are given on the individual use of probiotics and foods to improve the intestinal microbiocenosis [34]. The influence of the gut microbiome on the psychological state of a person and changes in its composition under the influence of physical activity is considered. Emphasis is placed on the additional intake of probiotic foods and fiber, which are usually limited in the diet of athletes [36–39]. These studies were conducted on adult athletes. However, this direction is extremely important in pediatric sports dietetics due to the high frequency of gastrointestinal disorders in children involved in sports [40].

The position of the International Society of Sports Nutrition (ISSN) on the use of the ergogenic drug creatine has been updated. Studies show that short-term and long-term supplements (up to 30 g/day for 5 years) are safe and well tolerated by adolescent athletes [41, 42].

ASSESSMENT OF THE DIET IN CHILDREN INVOLVED IN SPORTS

Given the high importance of nutrition in maintaining the health of athletes, studies have been conducted to evaluate their diet. Nutritional quality was assessed among athletes engaged in cyclic sports. The deficiency of energy value of the diet of various degrees of severity was found in almost half of the children, more often in the older age group. Insufficient intake of protein, PUFAs, calcium and excessive intake of saturated fatty acids was noted. The following factors were identified during the analysis of the causes of inadequate nutrition: excessive intensity and frequency of training, leading to non-compliance with the necessary meal regime (in almost all children); selective appetite (food preferences — when a child does not like certain foods) — in 67% of cases; food allergy or intolerance — in 22% of children. In assessing the nutrition of preschool children, it was found that many children at this age do not get enough fresh fruit, dairy products, cottage cheese, cheese and legumes, which, in turn, negatively affects their physical development. At the same time, there is a lack of knowledge about proper nutrition among both coaches and parents [43, 44]. Nutritional imbalance and inconsistency with physiological norms were also observed in children engaged in the least energy-consuming sport — chess. This is largely due to the failure to fulfill daily nutritional norms — the consumption of products in general is 12–13% lower than the norm, which leads to insufficient intake of protein, fat, minerals and vitamins [45]. Evaluation of macronutrients in the nutrition of junior soccer players (11–17 years old) revealed increased protein intake (1.8–2.0 g/kg per day), asignificant decrease in carbohydrate intake and a sufficient proportion of fat from the recommended values [46].

The studies on water balance in children engaged in different sports were also conducted. Bioimpedance analysis was used to determine the total amount of water in the body, taking into

account age and gender norms. A pronounced decrease in water content was found in young athletes engaged in hockey, martial arts, rhythmic gymnastics, and tennis (boys), which indicates noncompliance with the rules of the water intake [47].

Organization of nutrition in sports schools is an important aspect, revealing violations related to a meal regime, an increase in the amount of carbohydrate products or the absence of a canteen itself [48].

CONCLUSION

Thus, the nutrition of child athletes has significant differences due to the need to provide high requirements in nutrients, macro- and micronutrients and to compensate for energy expenditure associated with active physical activity. Adequate nutrition preserves health, optimizes performance, ensures the safety of muscle mass, prevents injury, promotes the recovery process after active physical activity, and increases sports results [49].

Knowledge of the basics of rational nutrition is necessary not only for sports medicine doctors, but also for pediatricians, teachers and coaches. It is of interest to develop computer programs to calculate the individual diet of each athlete. Such a program was developed at the Institute of Physiology of the Komi Scientific Center of the Ural Branch of the Russian Academy of Sciences (Russia), Syktyvkar (computer program "Sport: Calculation and Analysis of Ration" for calculation of nutritional and energy value of individual diets and further analysis of the obtained data). With its help it is possible to independently develop a diet with adequate nutritional and necessary energy value [50]. The development of such programs is a promising direction in the field of sportsmen's nutrition.

Foreign authors also pay much attention to research on the development of educational programs for athletes, parents and coaching staff, with the search for forms and methods for effective planning of sports diet [51, 52].

Rational nutrition will improve sports performance, recovery processes and adaptation to physical loads, will allow to achieve high results in sports while preserving the health of young athletes.

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 633.826+616.39-056.5-08+616.34-008.87-053.2+579.67
DOI: 10.56871/CmN-W.2024.45.37.006

CURCUMIN — PROSPECTS FOR USE IN THE TREATMENT OF DISEASES OF THE DIGESTIVE SYSTEM

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For citation: Nalyotov AV, Khavkin AI, Matsynin AN. Curcumin — prospects for use in the treatment of diseases of the digestive system. Children's Medicine of the North-West. 2024;12(3):49–56. DOI: https://doi.org/10.56871/CmN-W.2024.45.37.006

Received: 30.05.2024 **Revised: 26.06.2024** **Accepted: 10.09.2024**

Abstract. Inflammation underlies the development of most diseases. In recent years, more and more attention has been paid to curcumin, an active polyphenol found in turmeric root, which has numerous beneficial effects on the human body, including anti–inflammatory, anti-carcinogenic and antioxidant properties. Curcumin affects several cellular pathways and affects the composition of the gut microbiota. This review summarizes current information on the prospects of using curcumin in the treatment of inflammatory diseases of the digestive system.

Keywords*: curcumin, anti-inflammatory effect, therapy, intestinal microbiota, digestive system*

КУРКУМИН — ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ В ЛЕЧЕНИИ ЗАБОЛЕВАНИЙ ОРГАНОВ ПИЩЕВАРЕНИЯ

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Для цитирования: Налетов А.В., Хавкин А.И., Мацынин А.Н. Куркумин — перспективы использования в лечении заболеваний органов пищеварения // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 49–56. DOI: https://doi.org/10.56871/CmN-W.2024.45.37.006

Поступила: 30.05.2024 **Одобрена: 26.06.2024** **Принята к печати: 10.09.2024**

Резюме. Воспаление лежит в основе развития большинства заболеваний. В последние годы все больше внимания уделяется куркумину — активному полифенолу, содержащемуся в корне куркумы, который обладает многочисленными благотворными воздействиями на организм человека, включая противовоспалительное, антиканцерогенное и антиоксидантное свойства. Куркумин воздействует на несколько клеточных путей и оказывает влияние на состав микробиоты кишечника. В данном обзоре обобщены современные сведения о перспективах использования куркумина в терапии заболеваний пищеварительной системы.

Ключевые слова: *куркумин, противовоспалительный эффект, терапия, кишечная микробиота, пищеварительная система*

 ISSN 2221-2582

INTRODUCTION

Inflammation is a complex pathophysiologic process that is an adaptive response caused by exposure to a pathogenic stimulus, infection, or tissue damage to maintain the body's homeostasis. A long-lasting inflammatory process may participate in the pathogenesis of many chronic diseases, such as inflammatory bowel disease (IBD), obesity, diabetes mellitus, pancreatitis, cardiovascular pathology, metabolic disorders, arthritis, and others. The search for new effective compounds with anti-inflammatory effect without causing severe side effects from their use is an important task of current clinical researches.

This article will review the anti-inflammatory mechanisms of action of curcumin and the results of modern clinical studies devoted to its use in the therapy of diseases of the digestive system with emphasis on its effect on the state of the gut microbiome.

PHYSICAL AND CHEMICAL PROPERTIES OF CURCUMIN

Curcumin is a natural polyphenol which belongs to the curcuminoid family (compounds derived from *Curcuma longa L.*). Curcumin is known as the "golden spice of India". It has been used as an important medicinal herbal ingredient for thousands of years, and remains a popular dietary spice in many cuisines around the world. Nowadays, curcumin, an orange-yellow crystalline powder, is widely used in the food industry mainly as a coloring agent (E100) in food and beverage production.

Curcumin is considered to be one of the natural compounds with great potential in the treatment of various inflammatory diseases. This polyphenol has a beneficial effect on the composition of gut microbiota, antioxidant, antitumor and anti-inflammatory properties [1].

Curcumin is safe to take, as confirmed in human clinical trials. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) have established an acceptable daily intake for curcumin at 0–3 mg/kg of weight [2].

Curcumin is a low molecular weight lipophilic compound that is almost insoluble in aqueous physiological media. Its molecules can accumulate in cell membranes and act as an antioxidant by absorbing reactive oxygen species. The polyphenol remains fairly stable at low acidic gastric pH. It is rapidly metabolized by reduction, sulfation and glucuronidation in the liver, kidney and intestinal mucosa with low intestinal absorption after oral intake [3, 4]. Current evidence suggests that despite low absorption, curcumin may have beneficial health effects by maintaining high mucosal concentrations, modulating intestinal barrier function, and reducing high concentrations of bacterial lipopolysaccharides (LPS) [5].

BIOLOGICAL EFFECTS AND PHARMACOKINETICS OF CURCUMIN

For many years, limitations to the use of curcumin as a drug have been its chemical instability and poor systemic bioavailability with very low or almost undetectable concentrations in blood and extraintestinal tissues, as well as its rapid metabolism and systemic elimination. Finding an effective method of curcumin delivery for its use as a treatment for inflammatory diseases has been a challenge for researchers [6].

The most common way to increase the low pharmacokinetic profile of curcumin is its combination with the natural alkaloid of black pepper — piperine (Piper nigrum), which is a strong inhibitor of its glucuronidation process. Curcumin dispersed with colloidal nanoparticles (preparation "Teracurmin") showed high absorption capacity in studies on healthy volunteers [7]. Another example of improved bioavailability of curcumin is its inclusion in a micellar system [8]. There are also other combinations of curcumin: formula of turmeric powder and turmeric essential oil, lipid-curcumin formulations, combination of curcumin with lecithin.

The pronounced anti-inflammatory properties of curcumin, described for many years, have attracted great interest of researchers in the context of the treatment of diseases with a chronic inflammatory genesis. The transcription factor NF-κB is a universal regulator of the expression of immune response genes, apoptosis and the cell cycle. Disruption of NF-κB regulation causes the development of inflammation and autoimmune diseases. The anti-inflammatory effect of curcumin is mainly mediated by its ability to inhibit the intracellular NF-κB signaling pathway by blocking IkappaB (IkB) kinase, which leads to the prevention of cytokine-mediated phosphorylation and degradation of IkB, which is an inhibitor of NF-κB [9].

Signal transducer and activator of transcription (STAT) proteins are one of the molecular pathways involved in various biological processes such as cell proliferation and apoptosis. Curcumin

is able to increase the levels of anti-inflammatory cytokines and reduce inflammatory disease activity by inhibiting the expression of the JAK/STAT signaling pathway. In addition, studies suggest that this mechanism of curcumin is involved in reducing cancer cell migration and invasion [10].

Curcumin reduced the levels of pro-inflammatory mediators such as IL-1, IL-1β, IL-6, IL-8, IL-17, IL-27, TNFα, inducible nitric oxide synthase (iNOS) in inflammatory cell and animal studies. Curcumin has also been reported to inhibit the activity of proinflammatory proteins (activator protein-1, mitogen-activated protein kinases, peroxisome proliferator-activated receptor gamma (PPAR-γ), β-catenin) [11].

The NOD-like receptor protein 3 (NLRP3) inflammasome is a protein complex that regulates innate immune responses through the activation of caspase-1 and the expression of inflammatory cytokines. Curcumin can directly restrain NLRP3 inflammasome assembly or inhibit its activation, which may be one of the mechanisms for its application in the therapy of inflammatory diseases [9].

Curcumin has a regulatory effect on immune cells such as dendritic cells, T helper 17 (Th17), and regulatory T lymphocytes (Treg). Th17 are important pro-inflammatory cells that synthesize pro-inflammatory IL-17, IL-22, and IL-23. In turn, Treg have an inhibitory effect on the development of the inflammatory response. Alterations in the number and function of Th17 and Treg can induce an abnormal immune response leading to inflammation. Maintaining Th17/Treg balance helps to maintain immune homeostasis and treat inflammatory diseases. Curcumin has been found to inhibit Th17 differentiation and regulate the restoration of Th17/Treg balance [12].

Accumulation of reactive oxygen species in tissues leads to the development of oxidative stress, which increases inflammation by activating inflammation-related transcription factors. Curcumin reduces the production of reactive oxygen species due to its effect on nicotinamidadenine dinucleotide phosphatoxidase (NADPH) and increased activity of antioxidant systems [13].

CLINICAL APPLICATIONS OF CURCUMIN

Clinical studies investigating the efficacy of curcumin in the treatment of inflammatory diseases remain few to date.

M. Kato et al. used curcumin dispersed in colloidal nanoparticles to stimulate glucagon-like peptide-1 (GLP-1) secretion, resulting in increased insulin synthesis and secretion and better glycemic control in mice. This finding suggests a potential role for curcumin in the treatment of diabetes mellitus. However, the use of native curcumin did not lead to therapeutic results and did not improve glucose tolerance in mice [14].

Oral intake of curcumin results in its high concentration in the gastrointestinal (GI) tract, which has aroused great interest of researchers to study the effect of the polyphenol on the gut microbiota and to determine its role in potential benefit in the treatment of digestive system pathology [4, 15].

Several studies have investigated the properties of curcumin with respect to regulatory effects on the intestinal microbiome. Bacteria are actively involved in the metabolism of curcumin, leading to its biotransformation with the formation of metabolites, exerting local and systemic effects [38]. In turn, curcumin supplements stimulate the growth of beneficial bacterial strains, improve intestinal barrier function and reduce the expression of proinflammatory mediators [5, 16].

A. Hassaninasab et al. identified microorganisms with high metabolic activity against curcumin (*Escherichia coli* strain) and capable of converting it into dihydrocurcumin and tetrahydrocurcumin due to the presence of NADPH-dependent enzyme (CurA) [17]. In turn, the results of a study by S.D. Jazayeri et al. revealed that microorganisms such as *Bifidobacteria pseudocatenulaum, Enterococcus faecalis, Bifidobacteria longum, Lactobacillus acidophilus* and *Lactobacillus casei* are also capable of reducing the original curcumin compound by more than 50% and thus can participate in the metabolism of polyphenol [18].

L. Shen et al. in a study conducted in a mouse model found statistically significant changes ($p < 0.05$) in the number of *Prevotellaceae, Bacterioidaceae* and *Rikenellaceae* in the gut microbiome between individuals that received curcumin supplementation as part of nutrient formulas and mice from the control group that received a similar diet but without curcumin supplementation. The abundance of *Prevotellaceae* decreased and *Bacterioidaceae* and *Rikenellaceae* increased in individuals receiving curcumin supplementation relative to the control group [19].

W. Feng et al. in their study found that curcumin reduced fat deposition in the liver, improved intestinal barrier integrity and alleviated systemic endotoxemia in rats fed a high-fat diet. Curcumin also dramatically altered the overall structure of

the gut microbiota disrupted by the high-fat diet toward an intestinal composition characteristic of rats with reduced weight. The authors conclude that curcumin administration partially reduces the severity of hepatic steatosis through specific effects on the phylotypes of gut microbiota associated with its development [20].

Results of a randomized, double-blind, placebo-controlled trial published in 2021 showed that 8-week administration of curcumin extract was associated with improvement in gastrointestinal symptoms (abdominal pain, diarrhea, and constipation) in adults. Patients also showed a greater reduction in anxiety scores on the Depression Anxiety and Stress Scale (DASS-21). At the same time, curcumin supplementation had no significant effect on the degree of microbial diversity and the development of intestinal bacterial overgrowth syndrome [21].

The studied properties of curcumin with respect to the correction of bacterial species involved in the pathogenesis of inflammatory GI diseases may expand the understanding of the therapeutic potential of this polyphenol.

In a study by S.T. Peterson et al. conducted with 30 healthy subjects evaluated changes in the gut microbiota using 16S RNA sequencing after oral administration of turmeric at a dose of 6000 mg/day with piperine extract, curcumin at a dose of 6000 mg/day with piperine extract, or placebo initially, after 4 and 8 weeks. Both turmeric and curcumin were found to alter the gut microbiota in similar ways. Participants taking turmeric supplements had a 7% increase in the number of microbial species studied after treatment, while subjects receiving curcumin had an average 69% increase in the number of bacterial species studied. The authors indicated that the response of the gut microbiota to the conducted saplementation was personalized. Subjects who responded to the conducted therapy showed uniform increases in most species of *Clostridium* spp., *Bacteroides* spp., *Citrobacter* spp., *Cronobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Klebsiella* spp., *Parabacteroides* spp. and *Pseudomonas* spp. with decreases in the relative abundance of a few species of Blautia spp. and most species of *Ruminococcus* spp. [5].

Two independent studies investigated the modulating effect of curcumin nanoparticle administration on the colonic microbiota during colitis [22, 23].

In one study, R.M. McFadden et al. evaluated the efficacy of dietary supplementation with curcumin in a colitis-associated colorectal cancer mouse model. Curcumin supplementation resulted in increased survival of individuals and completely eliminated tumor burden. Against the background of the observed diet, there was an increase in bacterial diversity in the intestinal microflora with an increase in the relative abundance of *Lactobacillales* and a decrease in *Coriobacteriales*. The authors concluded that the favorable effect of curcumin on oncogenesis was associated with the correction of the imbalance of the gut microbiota [22].

Another study by M. Ohno et al. examined the effect of curcumin nanoparticle supplementation on colitis induced by dextran sodium sulfate (DSS) in mice. Curcumin supplementation was found to reduce the mRNA expression of inflammatory mediators in the colonic mucosa and NF-κB activation in colonic epithelial cells, increase the abundance of butyrate-producing bacteria by increasing its level in the feces [23], and modulate the intestinal barrier function through the assembly of tight contact proteins, activation of bocaloid cells [24, 25].

Y.M. Chen et al. studied the effects of curcumin extract nanoparticle supplementation (NCE-5x) on gut microbiota, physical fatigue, and performance in mice. The researchers found that supplementation with curcumin extract nanoparticles for 6 weeks changed the composition of the gut microbiota and led to reduced physical fatigue and increased performance in mice. Animals receiving curcumin extract showed a decrease in *Bacteroidetes* and an increase in *Firmicutes*. The authors concluded that curcumin can affect the gut microbiome, increasing tolerance to exercise [26].

A large number of studies have shown that changes in the gut microbiome are associated with the development of various metabolic diseases such as metabolic syndrome, obesity, diabetes mellitus and non-alcoholic fatty liver disease [27, 28]. The first study reporting the association between curcumin intake and gut microbiome diversity in a menopausal rat model was published in 2017. Its results showed that curcumin could partially reverse changes in rat gut microbiota biodiversity by altering the distribution of gut microbiota due to ovariectomy-induced estrogen deficiency. Curcumin administration increased the number of *Serratia, Shewanella, Pseudomonas, Papillibacter* and *Exiguobacterium* species and decreased the number of Anaerotruncus and *Helicobacter pylori* [29].

PERSPECTIVES OF THE USE OF CURCUMIN IN THE TREATMENT OF ULCERATIVE COLITIS

An interest in studying the efficacy of curcumin for the treatment of ulcerative colitis (UC) has increased markedly since 2020, as evidenced by the increasing number of published systematic reviews. S. Chandan et al. reviewed and analyzed seven clinical trials involving 380 patients with UC. The authors concluded that combination therapy based on mesalamine and curcumin almost 3-fold increased the chances of clinical response in patients relative to the group receiving placebo [30]. T. Zheng et al. in the analysis of the results of six clinical trials involving 349 patients with UC showed that therapy with mesalazine with curcumin supplementation is safe and effective with regard to the induction of clinical and endoscopic remission of the disease [31]. M.R. Coelho et al. in their systematic review analyzed six clinical trials involving 372 patients with UC. They studied the efficacy of curcumin supplementation for remission induction in patients with mild to moderate disease activity. The studies showed good tolerability of curcumin supplementation in combination with standard therapies. In addition, five out of six studies demonstrated good results associated with the achievement of clinical and/or endoscopic remission [32]. R.A. Goulart et al. in their meta-analysis studied four clinical trials involving 238 patients with mild to moderate UC, where they evaluated the efficacy of oral curcumin administration in relation to the induction of disease remission [33]. The authors concluded that the addition of curcumin as an adjunct to standard therapy for UC had a beneficial effect on the development of clinical remission in patients. A recent systematic review by J. Yin et al. evaluated the efficacy and safety of curcumin therapy in patients with UC and included six clinical trials with a total of 385 patients. The authors reported that curcumin supplementation in addition to standard therapy for UC may be an effective strategy for achieving clinical remission of the disease without causing the development of serious side effects [34].

CONCLUSION

Nowadays, data on the anti-inflammatory properties of curcumin are accumulating. Features of its metabolism and its effect on the state of gut microbiota allow us to consider the use of this polyphenol as a promising tool in the treatment of chronic inflammatory diseases of the digestive system. Further studies are needed to determine the effective dosage of curcumin, its effect on inflammation and composition of gut microbiota in patients with various gastrointestinal pathologies.

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 616.348-002.44-06+616.344-002-031.84+575.22+664.236+577.161.2
DOI: 10.56871/CmN-W.2024.11.68.007

GENETIC AND EPIGENETIC FACTORS IN THE GENESIS OF INFLAMMATORY BOWEL DISEASES

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For citation: Bogdanova NM, Kravtsova KA. Genetic and epigenetic factors in the genesis of inflammatory bowel diseases. Children's Medicine of the North-West. 2024;12(3):57–74. DOI: https://doi.org/10.56871/CmN-W.2024.11.68.007

Received: 16.03.2024 **Revised: 23.05.2024** **Accepted: 10.09.2024**

Abstract. Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by chronic inflammation in the gastrointestinal tract. The diseases have a multifactorial etiology, including genetic predisposition, gut microbiota, environmental factors, diet, lifestyle, and socioeconomic status. There is a steady increase in IBD throughout the world, especially in Scandinavia, North America, and Canada, Israel. The contribution of diet to the development and treatment of IBD is enormous. In 2020, the European Society for Enteral and Parenteral Nutrition (ESPEN) published recommendations on dietary management for IBD and provided information on the impact of food on the risk of developing diseases. It has been shown that the use of dairy products may have a predominantly protective effect in the etiology of CD and UC, although a clear dose-response relationship has not been established; Gluten is capable of triggering innate and adaptive immune responses responsible for intestinal inflammation. In addition, there are reports that point to celiac disease as a potential risk factor for IBD. Evidence is presented that the microbiota and vitamin D play an important role in stimulating and regulating the immune system. In turn, intestinal dysbiosis observed in patients with IBD may be either a cause of local intestinal inflammation or potentially one of the factors leading to chronic inflammation in IBD, as well as vitamin D deficiency.

Keywords*: inflammatory bowel diseases, Crohn's disease, ulcerative colitis, genetics, genotype, dairy products, gluten, celiac disease, microbiota, vitamin D, vitamin D receptor*

ГЕНЕТИЧЕСКИЕ И ЭПИГЕНЕТИЧЕСКИЕ ФАКТОРЫ В ГЕНЕЗЕ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА

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Для цитирования: Богданова Н.М., Кравцова К.А. Генетические и эпигенетические факторы в генезе воспалительных заболеваний кишечника // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 57–74. DOI: https://doi.org/10.56871/CmN-W.2024.11.68.007

Поступила: 16.03.2024 **Одобрена: 23.05.2024** **Принята к печати: 10.09.2024**

Резюме. Воспалительные заболевания кишечника (ВЗК) объединяют язвенный колит и болезнь Крона, которые характеризуются хроническим воспалением в гастроинтестинальном тракте. Заболевания имеют многофакторную этиологию, включая генетическую предрасположенность, микробиоту кишечника, факторы окружающей среды, диету, образ жизни и социально-экономический статус. Во всем мире наблюдается неуклонный рост ВЗК, особенно в странах Скандинавии, Северной Америке, Канаде, Израиле. Вклад диеты в развитие и лечение ВЗК огромен. В 2020 году Европейское общество парентерального и энтерального питания (ESPEN — European Society of Parenteral and Enteral Nutrition) опубликовало рекомендации по

диетотерапии при данной патологии и представило информацию о влиянии еды на риск развития данных заболеваний. Показано, что использование молочных продуктов может иметь преимущественно защитный эффект в этиологии как болезни Крона, так и язвенного колита. Хотя четкой зависимости «доза–реакция» не установлено, глютен способен запускать врожденный и адаптивный иммунный ответ, ответственный за воспаление кишечника. Кроме этого, имеются сообщения, которые указывают на целиакию как на потенциальный фактор риска ВЗК. Представлены доказательства того, что микробиота и витамин D играют важную роль в стимуляции и регуляции иммунной системы. В свою очередь, дисбиоз кишечника может быть либо причиной локального воспаления кишечника, либо одним из потенциальных факторов, приводящих к хроническому воспалению, так же как и дефицит витамина D.

Ключевые слова: *воспалительные заболевания кишечника, болезнь Крона, язвенный колит, генетика, генотип, молочные продукты, глютен, целиакия, микробиота, витамин D, рецептор витамина D*

INTRODUCTION

Inflammatory bowel disease (IBD) unites two main clinical entities: ulcerative colitis and Crohn's disease, which are characterized by chronic inflammation in the gastrointestinal tract [1]. The diseases have a multifactorial etiology, including genetic predisposition, gut microbiota, environmental factors, diet, lifestyle and socioeconomic status.

In high-income countries, the epidemiology of IBD is associated with modernization and Western lifestyle (consumption of mostly refined foods rich in saturated fats and low consumption of vegetables, fruits). The growth of morbidity in developing countries is predetermined by rapid urbanization, industrialization, increasing levels of anxiety, as well as westernization of the population, dietary changes (primarily, an active consumption of gluten-containing products) [2]. In addition, the "Western type of nutrition" is characterized by excessive consumption of animal protein, saturated fats, salt, alcohol with a simultaneous decrease in vegetables and fruits in the diet.

There are significant differences in the epidemiology of IBD worldwide. They are maximally frequent in Scandinavian countries, North America, Canada, Israel. Thus, the annual increase in morbidity in Europe per 100,000 citizens is: for ulcerative colitis — 5–20 cases, for Crohn's disease — 5–10 cases with a clear upward trend. The diseases predominantly affect young people, with an average age of 20–40 years, although they can debut at any age. Currently, in some countries there is a tendency to increase the prevalence of ulcerative colitis in the older age group (the second peak of morbidity occurs after 60 years), and Crohn's disease — in childhood. Men and women have approximately the same morbidity [3].

In the Russian Federation, the incidence of IBD is poorly studied. Large-scale epidemiologic studies conducted in Russia indicate that the prevalence of this pathology corresponds to the average figures for Central Europe. Unfortunately, unlike most European countries, in the Russian Federation, severe, complicated forms of disease with a high percentage of mortality predominate. Scientists consider late diagnosis to be one of the reasons for this unfavorable situation. On average, from the onset of inflammatory process in the gastrointestinal tract to diagnosis it takes from 2 to 6 years [4].

In addition, a number of comorbid pathologies contribute to the negative course of diseases, as patients often suffer from protein-energy deficiency, sarcopenia and deficiency of essential micronutrients (vitamins, vitamin-like compounds, micro- and macronutrients). This is due to the fact that against the background of chronic inflammation, some patients are afraid to eat in order not to cause an exacerbation and (or) not to intensify the already existing symptoms of digestive discomfort. Other patients suffer from different variants of food intolerance, also with the development of dyspeptic and painful symptoms. For both the former and the latter, it is significantly limit their dietary intake of certain food groups.

In children, malnutrition leads to disorders of puberty, connective tissue synthesis and growth retardation. For example, growth retardation at the diagnosis of Crohn's disease and ulcerative colitis has been reported in 10–56% and 3–10% of children, respectively [5].

Malnutrition can manifest as overweight, obesity and even the development of sarcopenia in obesity. According to a systematic review including 783 children with IBD, low body mass index (BMI) (nutritional deficiencies of varying severity) was observed in Crohn's disease in 22–24% of cases. In ulcerative colitis it was observed in 7–9% of cases. BMI corresponding to overweight and obesity was found in 10% and 20–30% of children, respectively [6].

Another very important aspect that aggravates the course of IBD diseases and contributes to the negative outcome is the imbalance in the consortium of microorganisms with perverted immune response [3].

Thus, unbalanced and insufficient nutrition both in terms of basic nutrients and energy and micronutrients alters the homeostasis of the organism and causes dysbiotic state, microelementosis, hypovitaminosis and inflammatory reactions. All of this conditions have a negative impact on the processes of DNA methylation, acetylation and non-coding RNA (ncRNA), contributing to the formation of IBD in genetically predisposed individuals [7].

GENETIC FACTORS IN THE FORMATION OF INFLAMMATORY BOWEL DISEASE

Genome-wide association studies (GWAS) have identified more than 240 genetic loci associated with IBD in humans. The polygenic nature of inheritance has been shown. HLA genes *B40, DR3, DR5, DQ2, DR1*3, CV4* play a certain role in this. The polymorphism *Ala893* — multidrug resistance gene *(MDR1)* and mutation of *IBD5 and CARD15 (NOD2)* genes on chromosome 16 were revealed.

NOD2 protein takes part in the formation of the epithelial protective barrier. Mutation of the corresponding gene leads to a decrease in the synthesis of defensins by Paneth cells and impaired intestinal protective function with penetration of intestinal bacteria into the mucosal cells and the formation of inflammation.

Mutations of the *CARD15 (NOD2)* gene are more common in patients with Crohn's disease and are associated with the development of terminal ileitis complicated by stenosis. There are data on the predominant role of the *HLA B40* gene in the ontogenesis of the disease in elderly people and *HLA DR5* and *CV4* genes in young patients [8].

The majority of IBD genetic associations were obtained in a study of individuals of European (EUR) origins. The sample of the East Asian population (EAS) for determining genetic mutations has a much smaller size [9].

A huge contribution to the study of the genetic architecture associated with human IBD belongs to a group of scientists headed by Z. Liu (2023) who identified 16 new genetic loci in the ancestors of the East Asian population (China, Korea, and Japan) and determined the variance (diversity of traits in the population) of 81 genetic loci in the ancestors of Asian and European origin.

The identified phylogenetic variance was mainly explained by higher minor allele frequencies (MAFs) in Asians rather than equal effect sizes [10]. In addition, researchers found comparable factor inheritability based on single nucleotide polymorphism among European and Asian individuals of previous generations. It is indicating that the magnitude of genetic contribution to disease is almost identical in both populations and that many IBD genetic loci are identical except for some such as tumor necrosis factor 15 (TNF15), colony stimulating factor 2 receptor subunit beta(CSF-β 2R) and IL-23 receptors [11].

Because the variance explained by IBD loci differs by great-grandparent (ancestral) territory, the ability to profile genes and predict risk for Crohn's disease and ulcerative colitis in humans also varies widely. Z. Liu et al. (2023) evaluated this ability using polygenic risk score (PRS) and observed that PRS trained in the EUR population has lower accuracy in the EAS population. The scientists believe that their discovery will allow a better understanding of the genesis of IBD and provide a personalized approach to the therapy [10, 11].

EPIGENETIC FACTORS IN THE ONTOGENESIS OF INFLAMMATORY BOWEL DISEASE

Diet

In both children and adults with IBD, certain dietary interventions have been shown to improve clinical symptoms and reduce the inflammatory burden. However, it is not clear how food and individual food components are involved in the pathogenesis of intestinal damage in IBD. Assessing the effects of diet on disease course is complex because, regardless of the dietary pattern adopted, each diet is based on the consumption of many different food groups that influence each other.

A study conducted in Ireland demonstrated that IBD patients resorted to dietary restrictions in the hope of preventing relapse in 85% of cases, including: avoiding fatty foods in 68%, spicy foods in 64%, and raw vegetables or fruits in 58%. In turn, eating a low-fiber food during relapse reduced the symptoms of the disease in 74% of patients [12].

In other words, it should be assumed that some components of a particular product have a proinflammatory potential and can change the vector of immune response towards mucosal inflammation, characteristic of IBD, and at the same time distort the motor function of the intestine. For example, restriction of foods with high levels of dietary fiber in the diet is accompanied by a decrease in bacterial fermentation and gas formation and contributes to digestive comfort [13].

Although the exact mechanism of the effect of "Western diet" on the body is unknown, the effect of some nutrients on the genesis of IBD has been well studied. For example, the effect of saturated fat on toll-like receptors type 2 and 4 (TLR-2 and TLR-4), which are located on immune cells in the intestine and are responsible for signaling from bacteria. Thus, consumption of fried foods with an abundance of saturated fats induces TLR and causes expansion of inflammation in the epithelium of the digestive tube. In contrast, polyunsaturated fatty acids (PUFAs) reduce TLR expression and have the opposite effect.

A number of amino acids found in the products, such as arginine and glutamine, stabilize the intestinal barrier function and increase the synthesis of mucin, which has a protective effect against the intestinal mucosa.

Fatty and sweet foods disrupt the structure of the gut microbiome, increasing intestinal permeability and enhancing the systemic inflammatory process. In turn, the use of prebiotic foods proliferates the indigenous microbiota, which increases levels of short-chain fatty acids, particularly butyrate (butyric acid), in the GI tract. This acid stabilizes the intestinal barrier by regulating the permeability of the colonic mucosa, inhibits oxidative stress, exerts anti-inflammatory effects and carries out prevention of colorectal carcinogenesis [14]. At the same time, abnormal production of butyrate by the microbiome is recognized as the cause of higher expression of the non-functional form of FOXP3, which is associated with an increased risk of autoimmunity [15].

In 2020, the European Society of Parenteral and Enteral Nutrition (ESPEN) published recommendations on dietary therapy for IBD and provided information on the influence of food on the risk of disease development:

- the threat is reduced with a diet rich in fruits and vegetables, omega-3 fatty acids with restriction of omega-6 fatty acids;
- the risk of Crohn's disease, but not ulcerative colitis, is lower with a diet high in fruit and dietary fiber (more than 22 g/day).

This paper also indicates that breastfeeding should be prolonged to at least 6 months, as randomized clinical trials and meta-analyses have shown that this reduces the likelihood of IBD later in life [16, 17].

The journal Gastroenterology (2020) published an analysis of a large cohort of patients (166,903 women and 41,931 men) who were followed-up prospectively for 25–30 years. For each patient, an empirical dietary inflammatory pattern index (EDIP) was determined from a nutritional questionnaire, which is calculated based on the effect of each type of food on the concentration of inflammatory markers. According to the data obtained from the questionnaires, it was found that individuals who developed Crohn's disease were more likely to use foods with a high inflammation index in their diet. No such correlation was found in patients with ulcerative colitis [18].

The construction and validation of the nutrition model recorded a strong correlation between the empirical inflammatory index and three inflammatory markers determined in blood plasma: IL-6, C-reactive protein (CRP) and TNFaR2, as well as adiponectin and the overall assessment of inflammatory markers [18, 19].

Thus, the current level of knowledge allows us to consider that diet is not only a risk factor for IBD because of its role in the induction of intestinal dysbiosis and aberrant mucosal immune response in genetically predisposed people, but also a potential tool in the treatment of that disease [20, 21].

Dairy products

Both molecular and clinical studies demonstrate that components of dairy products have an inverse relationship with sluggish inflammation and affect key cytokines such as tumor necrosis factor alpha (TNFα) [22]. It has been observed that saturated fats in milk induce inflammatory processes through cytokine gene expression and composition of lactic acid bacteria in the gut [23]. A recent study in mice demonstrated that milk triglyceride consumption alters the composition of bile acids and the microbial community with an inversion of inflammation, i.e., the development of colitis [24].

In an experimental study conducted under the supervision of C. Garcia (2022) studied the role

that milk polar lipids (MFGM) — phospholipids (PLs) and sphingolipids (SLs) — have on colitis activity induced by 1% dextran sulfate sodium solution, colonic transcriptome and gut microbiome. It was found that saplementation of diets high in milk polar lipids had a protective effect. Diets low in milk polar lipids had a dual effect. During the period of colitis exacerbation, polar lipids weaken the disease activity. During the recovery period they cause an increase in disease symptoms and inflammation [25].

Thus, polar lipids in milk should be considered as a nutritional matrix factor that can directly provide health benefits and influence the actions of other dietary fats [25, 26].

A group of authors led by S. Talebi (2023) presented a meta-analysis on the association between different sources of dietary protein (general and animal protein) and the incidence of IBD in the population, which showed that higher consumption of dairy products has a protective effect on the risk of IBD formation. Although the researchers did not observe an association between different sources of animal protein and disease risk, a dose-effect analysis found that a 100 g daily increase in meat in the diet was associated with a 38% increase in IBD risk. Moreover, a positive linear correlation was found between total meat consumption and the likelihood of IBD (Pnonlinearity=0.522, Pdose-response=0.005) [27].

Several retrospective 'case-control" studies have reported either no or a small inverse association between dairy products and IBD risk [28, 29].

Recently, the GBD (Global Burden of Disease) staff published data on the prevalence of IBD in each country and noted that Switzerland, a country famous for cheese production and consumption, has a low incidence of IBD, while the UK and the USA, where the population eats relatively little cheese, have a high incidence of the disease. Thus, it has been shown that utilization of milk and/or dairy products (cheese or yogurt) has a negative correlation with the epidemiology of IBD at the national level in Western countries [30].

A large European prospective cohort study involving 401,326 participants noted a correlation between the use of dairy products (milk, yogurt and cheese) prior to diagnosis and the subsequent development of Crohn's disease and ulcerative colitis. When participants were recruited, their dairy product absorption was determined using validated food frequency questionnaires. The results of this study demonstrate that milk consumption may have a predominantly protective effect in the etiology of these diseases, although no clear dose-response relationship has been established [31].

Somewhat different information is presented in the work of K.Y. Tsai et al. (2023). The authors evaluated the effect of dairy products on the course of ulcerative colitis in patients with pre-existing disease and diagnosed for the first time disease. The authors' conclusions suggest that restricting the dairy diet first and then eliminating trigger factors (medicinal herbs/Chinese tonic products, nutritional supplements, psychological problems, non-dietary factors, namely smoking cessation, cosmetic products and stopping medications by patients themselves in case of disease recurrence) will help to improve disease control and reduce the prescription of medications to patients with ulcerative colitis in daily clinical practice [32].

In a multicenter cross-sectional study involving 12 gastroenterology centers from four countries, scientists needed to determine whether it was really necessary to deprive patients with IBD of dairy product consumption. The study included 872 patients with IBD, 1016 cases without it. In all respondents in comparison, during 6 months, symptoms from the digestive system after consumption of dairy products were evaluated. Based on the material obtained, the authors concluded that there is no convincing data on the negative effect of dairy products on the course of inflammation in the intestine, and, accordingly, dairy products should not be excluded from the diet of IBD patients [33].

Gluten

Gluten is a protein composed of gliadins and glutenins found in most cereals such as barley, wheat and rye [34, 35]. In recent decades, an increasing number of adverse reactions after gluten consumption have been reported in the literature, categorized as IgE-mediated wheat allergy, celiac disease and non-celiac gluten sensitivity (NCGS) [2, 35].

There is a growing number of studies proving that gluten can trigger an innate and adaptive immune reaction responsible for intestinal inflammation. Together with other dietary elements, gluten may contribute to the development of IBD, functional gastrointestinal disorders (FGID) and exacerbation of symptoms in these pathologies. Although the exact role of gluten in the genesis of these conditions remains unclear, at least 50 dif-

ferent gliadin epitopes have been identified that play immunomodulatory and cytotoxic roles, as well as determine intestinal permeability through reorganization of actin filaments and modified expression of connective complex proteins such as zonulin [36]. Some of these epitopes stimulate a pro-inflammatory innate immune response, while others activate specific T cells. K. Ziegler et al. (2019) that amylase and trypsin inhibitors found in cereals containing gluten have the ability to activate TLRs, thereby stimulating the release of inflammatory cytokines and inducing a T-cell immune response [37]. In addition, gliadin induces an inflammatory response by synthesizing a variety of pro-inflammatory cytokines (IL-6, IL-8, IL-13 and INF-1, IL-23, IL-1β and TNFα) [36].

More than half of IBD patients believe that their symptoms are aggravated by certain foods, particularly gluten containing foods [38]. Currently, a gluten-free diet is not recommended for patients with IBD. However, various sources discuss that patients eliminate gluten from their diet to alleviate gastrointestinal symptoms, although there is still no scientific evidence for this [39].

In the article by N. Morton et al. (2020) it is stated that 66% of patients showed improvement of gastrointestinal symptoms, and 38% of patients showed a decrease in the frequency and severity of their exacerbations on a gluten-free diet [38]. The same conclusion was made 10 years earlier by C.M. Triggs et al. (2010), although their work focused on food intolerance. They noted that specific dietary changes in the majority of subjects (>66%) reduced the number of exacerbations and the severity of gastrointestinal symptoms. In particular, it was reported that gluten-free foods often contributed to symptom reduction and were least associated with side effects [40].

C. Zallot (2013) offered 244 adults with IBD to fill out a 14-item questionnaire. After its analysis he noted that even if 9.5% of these patients believed that gluten exclusion helps to improve symptoms during exacerbations of the disease, only 1.6% actually decided to do so during its relapse [41].

A similar conclusion was made by a group of authors after a questionnaire survey of 1254 IBD patients. They indicated that patients who followed a gluten-free diet (4.7%) experienced no differences in disease activity, complications, and frequency of hospitalizations compared to patients who did not follow a certain dietary regimen. In addition, the authors noted a worsening of psychological well-being in those who followed the diet [42].

These controversial results emphasize the importance of further research, as there is still insufficient evidence to recommend the elimination of gluten from the diet of these patients, mainly because this protein is likely to be only one of many factors involved in the clinical symptoms of IBD.

At the same time, gluten-free industrial products are saturated with salt, fat, and sugar. This makes them more palatable to customers. This composition has nutritional properties of low quality and is associated with an increase in cardiovascular disease. In addition, it can predispose to inflammatory and functional gastrointestinal diseases. Finally, the absence of gluten in the diet may have a negative impact on the psychological well-being of these patients secondary to the restrictive characteristics of the diet itself. Although these data are intriguing, further research is needed before any recommendation for gluten avoidance can be made.

CELIAC DISEASE IS A RISK FACTOR FOR INFLAMMATORY BOWEL DISEASE

Celiac disease, a chronic immune-mediated enteropathy that develops as a consequence of gluten consumption, shares with IBD a multifactorial etiology resulting from a complex interaction between genetic variability, environmental factors, and dysregulation of the immune response [43].

A. Shah et al. (2019) pointed out celiac disease as a potential risk factor for IBD and demonstrated that IBD occurs more frequently in patients with celiac disease compared to the general population [44]. Children with co-morbidities (IBD and celiac disease) have been found to have specific phenotypic features with a higher risk of autoimmune diseases, colectomy and delayed puberty compared to children with IBD only [45].

A study conducted by S. Yehuda et al. (2019) showed that patients with IBD were more likely to suffer from various autoimmune diseases compared to patients without IBD [46]. In a retrospective analysis by M. Alkhayyat (2021) emphasized the significant association between celiac disease and IBD. It was noted that in ulcerative colitis the risk of celiac disease formation is higher compared to the occurrence of other autoimmune diseases [33].

E. Aghamomadi et al. (2022) found a similar pattern of expression of proinflammatory cytokines in intestinal biopsy samples from both individuals with celiac disease and IBD. Thus, these findings bring new perspectives in the search for

common potential biomarkers for diagnosis and common therapeutic targets for the treatment of these diseases [47]. Although an earlier study in adults with IBD (n=1711) was able to confirm histologically and serologically the diagnosis of celiac disease in only 0.5% of them [48].

MICROBIOME

The microbiota has been proven to play an important role in the stimulation and regulation of the immune system [49]. Dysbacteriosis observed in patients with IBD may be either the cause of localized intestinal damage or potentially one of the factors leading to chronic inflammation.

The study of the gut microbiota has revealed significant differences in healthy and IBD subjects. In IBD, a less rich composition of commensals is observed against the background of increased mucose-associated microbiota. The structure of the intestinal microcosm is characterized by a decrease in the number of representatives of the phyla *Bacteroidetes* and *Firmicutes*, which have anti-inflammatory activity. It also shows an increase in the titer of microorganisms of the phyla *Enterobacteriaceae* (in particular, *E. coli,* and its invasive strains). Specific microbiota markers of IBD have even been identified, namely, the predominance of *Enterobacteria, Proteobacteria,* adhesive *E. coli* and the deficiency of *Cl. coccoides, Faecalibacterium* [50–52].

It has been noted that during IBD exacerbation the concentration of *Bifidobacterium* spp. and *Lactobacillus* spp. is suppressed compared to remission periods. In addition, differences in the composition of microbiota have been found in IBD patients. Firstly, it was found between inflammatory and non-inflammatory regions of the intestine [53]. Secondly, it depended on the localization of the pathological process, for example, in Crohn's disease with lesions of the colon and ileum. Moreover, it has been found that in patients with ulcerative colitis, one serotype of *Escherichia coli* dominates over the other fecal microbiota [54].

The combination of imbalance between the commensal and aggressive microbiota, as well as impaired epithelial permeability, leads to perversion of the recognition of pathogen-associated molecular structures by toll-like receptors (TLRs). This is accompanied by pronounced endotoxemia, disinhibition of the early phase of inflammation and formation of specific antibodies.

It has been suggested that the causes of dysbiosis in IBD patients may be colonization of the intestine by pathogenic microorganisms, failure of immunological tolerance to their own microorganisms, or a combination of both [54].

Patients with ulcerative colitis more often have induction of Th2-lymphocytes and NKT (natural killer T cells) with high concentration of IL-4 and IL-13 with insufficient suppressor function of regulatory T cells (T-reg) and their cytokines (TGF-β and IL-10), while patients with Crohn's disease express Th1- and Th17-lymphocytes and increase the level of IL-12, IL-17, IL-23 and gamma interferon (INF-γ). It has been observed that an increase in pro-inflammatory cytokines correlates with a decrease in short-chain fatty acids [14].

Considering gluten as one of the triggering factors in the genesis of IBD, it is necessary to emphasize the microbiota. The microbiota of patients on a gluten-free diet has been found to be more similar to the healthy gut microbiome compared to the microbiota of gluten-consuming patients [55].

Lactobacillus spp. are recognized as the leading microbial species in the structure of a healthy microbiota, as they break down gluten peptides, thereby reducing their immunogenicity. The protective role of *Lactobacillus* spp. was confirmed by the work of Herrán et al. In this study, it was emphasized that this bacterium is directly involved in the process of gluten digestion, thus inactivating its immunomodulatory and cytotoxic effects on intestinal cells [56].

It has been proposed to modulate the microbiota of IBD patients with probiotics to avoid disease progression and/or reduce the intensity of the active phase.

Several studies evaluating probiotics in IBD patients have shown encouraging results. For example, the probiotic composition VSL#3, which contains *Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus debrueckii sub. Bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis* and *Streptococcus salivarius sub. Thermophilus* improved clinical symptoms in patients suffering from ulcerative colitis [57, 58].

Recent studies on inflammatory biomarkers have shown that consumption of fermented dairy products transforms the fecal microbiota and reduces markers of systemic inflammation [59–62].

The administration of fermented dairy products which contains *Bifidobacteria infantis, Bifidobacterium* breve, *Bifidobacterium bifidum* and *Lactobacillus acidophilus* provided clinical and endoscopic improvement in patients with ulcera-

tive colitis, as they had decreased plasma IL-6 concentrations compared to placebo. The effect of probiotic fermented milk products approached that of probiotics [63].

Additional prospective multicenter studies are needed to draw a final conclusion about the effectiveness of fermented dairy products in IBD.

THE ROLE OF VITAMIN D IN THE GENESIS OF INFLAMMATORY BOWEL DISEASE

Epidemiologic studies indicate that vitamin D deficiency (VDD) is widespread among patients with IBD. For example, the diseases have been found to be more common in countries of northern latitudes than in southern latitudes, which is consistent with vitamin D deficiency among the inhabitants of these regions [64].

It is well known that the production of this vitamin in the subcutaneous fat layer depends on exposure to UVB radiation through sunlight, and in climate and geographical zones located above the 60th meridian, the number of clear days is limited, and the wavelength range of UVB radiation does not provide the synthesis of vitamin D.

Due to its immunomodulatory properties, vitamin D contributes to the adequate functioning of the innate and adaptive immune response, including anti-inflammatory effects, modulating the activation, proliferation and differentiation of T- and B-cells, maintaining the integrity of the intestinal barrier and the composition of the gut microbiota. In turn, vitamin D deficiency is associated with increased susceptibility to immune-mediated diseases, including IBD [65, 66]. Low vitamin D range has been shown to correlate with disease acuity, frequent hospitalization, clinical and postoperative relapses, lack of response to biologic drugs, and poor quality of life [67, 68].

An association between IBD and single nucleotide polymorphisms (SNPs) associated with vitamin D deficiency and vitamin D receptor (VDR) has been identified [69–71].

However, in clinical studies that have demonstrated an association of low vitamin D concentrations with clinical relapse of IBD, current data have failed to establish a conclusive genetic association between the single nucleotide polymorphism of vitamin D deficiency and the vitamin D receptor with IBD [72].

A meta-analysis of several studies evaluated the interference of the VDR gene polymorphism, which is mapped to a region of chromosome 12, on the risk of ulcerative colitis and Crohn's disease. The vitamin D receptor serves as a cellular receptor for calcitriol, which exerts a wide range of different regulatory effects on the immune system [73].

Four allelic polymorphisms of the *VDR* gene *(rs731236, TaqI; rs1544410, BsmI; rs2228570, FokI; rs17879735, ApaI)* were investigated. The study finds that European carriers of *rs731236 TaqI tt* have an increased likelihood of Crohn's disease, while the presence of the *ApaI* allele reduces this risk in both Europeans and Asians. The presence of the *FokI* allele determines susceptibility to ulcerative colitis only in Asians [73].

A New Zealand study analyzed the role of serum vitamin D levels in individuals with a certain genotype on the status of Crohn's disease. Researchers found that the concentration of vitamin D in serum is significantly lower in this disease compared to healthy individuals. The presence of the allele *rs731236-A (VDR)* or *rs732594-A (SCUBE3*) in Crohn's disease had a clear correlation with vitamin D supply [74].

Low levels of vitamin D receptor are coordinated not only with chronic inflammation but also with reduced expression of the *ATG16L1* gene, which is required for autophagy and maintenance of intesti-nal homeostasis. In addition, the *ATG16L1* gene also accounts for the innate and adaptive response through the expression of dendritic cells (DCs), T- and B-lymphocytes. Recently, the vitamin D receptor has been shown to regulate *ATG16L1* gene transcription [75]. Moreover, the vitamin D-VDR complex plays a crucial role in maintaining the integrity of the intestinal barrier by inducing transcription of the gene encoding the enzyme proteintyrosine phosphatase N2 (PTPN2), which suppresses the expression of claudin-2 (a protein that increases intestinal permeability). This mechanism helps to prevent intes-tinal inflammation [76, 77].

Antimicrobial peptides such as cathelicidin and defensins also provide protection to the intestinal barrier. Vitamin D increases cathelicidin synthesis in macrophages by interacting with receptors located in the promoter region of the gene responsible for the synthesis of this protein. Vitamin D deficiency is associated with inhibition of cathelicidin expression and, consequently, with increased development of the inflammatory process [78].

CARD15/NOD2, the major IBD-related gene, is structurally similar to innate immunity proteins. The *CARD15/NOD2* gene is predominantly localized in monocytes, macrophages and dendritic cells, but can be expressed in enterocytes after activation by inflammatory cytokines (TNFa or IFN-γ) [78].

Vitamin D stimulates the expression of the *CARD15/NOD2* gene and the protein of the same name in epithelial and monocytic cells. This triggers the NF-κB pathway and enhances the antimicrobial defense of β2-defensin and cathelicidin in the presence of muramyl peptide. However, this effect is only observed in individuals with functional NOD2 protein, as Crohn's disease patients homozygous for non-functional NOD2 variants do not show this response. A significant number of mutations associated with Crohn's disease are characterized by reduced NF-κB activation when exposed to muramyl dipeptide. This observation implies that impaired anti-inflammation involving *CARD15/NOD2* may play a role in the pathogenesis of Crohn's disease or some other inflammatory disease, as the vitamin D deficiency [78].

Vitamin D is able to inhibit the IL-23 receptor pathway in innate lymphoid cells (ILC- 3), which are tissue-resident lymphocytes that functionally resemble T helper cells 17/22 in the adaptive system [79].

Circulating B cells can regulate the immune response by producing vitamin D through an autocrine mechanism, thus preventing the cascade of inflammatory reactions [80].

CONCLUSION

IBD is steadily increasing worldwide. An important role in the emergence of IBD belongs to epigenetic processes, which, in the presence of genetic predisposition, realize the effect of provoking (trigger) factors, namely, through the restructuring of the immune response form the inflammatory phenotype.

It is now proven that the widespread westernization of eating behavior leads to a significant transformation of the gut microbiome, affecting the activity of immunomodulatory genes such as *TGFβ, TGFβR, CTLA4, FOXP3*, contributing to the formation of a pro-inflammatory phenotype and a wider spread of chronic inflammatory and autoimmune diseases. Vitamin D deficiency can alter DNA methylation processes associated with genes regulating metabolic and immune functions. These disorders affect transcriptional activity and gene expression levels, determining the risk of IBD development and its course.

Thus, prevention of IBD in the presence of genetic predisposition should be aimed at a healthy lifestyle, adequate nutrition, preservation of the microbiome with constant monitoring of the immune status.

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 616.344-002-031.81-07+615.06+581.41
DOI: 10.56871/CmN-W.2024.64.86.008

UPPER GASTROINTESTINAL MORPHOLOGICAL CHANGES IN CROHN'S DISEASE (LITERATURE REVIEW)

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For citation: Permyakova AA, Trapeznikova AYu. Upper gastrointestinal morphological changes in crohn's disease (literature review). Children's Medicine of the North-West. 2024;12(3):75–80. DOI: https://doi.org/10.56871/CmN-W.2024.64.86.008

Received: 29.05.2024 **Revised: 01.07.2024** **Accepted: 10.09.2024**

Abstract. In 1932, Burrill Bernard Kron, Leon Ginsberg and Gordon Oppenheimer published an article entitled "Regional Ileitis:Pathological and Clinical Essence", in which they first described terminal ileitis, later named B. Kron. Crohn's disease (CD) is a recurrent systemic inflammatory disease affecting the gastrointestinal tract with extraintestinal manifestations and systemic immunological disorders. It can be localized in all parts of the gastrointestinal tract and is characterized by a variety of intestinal and extraintestinal manifestations, which depend on the depth, length of the affected organ and the characteristics of immune (systemic) complications. Upper gastrointestinal tract lesions in this disease are an understudied area. Routine screening showed a higher prevalence of the described pathology among children compared to adults. Upper gastrointestinal involvement in Crohn's disease is an understudied area. Routine screening showed a higher prevalence of this pathology among children compared to adults. In most patients, damage to the upper gastrointestinal tract remains asymptomatic, but pathological changes in the mucous membrane, diagnosed by morphological examination, are possible. In routine practice, endoscopic examination is recommended for patients with pre-existing lesion symptoms. This literature review considers morphological changes in the upper gastrointestinal tract in Crohn's disease, which are a consequence of both the underlying disease and the side effects of drugs used in the treatment of this pathology.

Keywords: *inflammation, morphology, Crohn's disease*

МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ВЕРХНИХ ОТДЕЛАХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА ПРИ БОЛЕЗНИ КРОНА (ОБЗОР ЛИТЕРАТУРЫ)

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Для цитирования: Пермякова А.А., Трапезникова А.Ю. Морфологические изменения в верхних отделах желудочно-кишечного тракта при болезни Крона (обзор литературы) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 75–80. DOI: https://doi.org/10.56871/CmN-W.2024.64.86.008

Поступила: 29.05.2024 **Одобрена: 01.07.2024** **Принята к печати: 10.09.2024**

Резюме. В 1932 г. Беррилл Бернард Крон, Леон Гинзберг и Гордон Оппенгеймер опубликовали статью «Региональный илеит: патологическая и клиническая сущность», в которой впервые описали терминальный илеит, получивший в дальнейшем имя Б. Крона. Болезнь Крона (БК) — рецидивирующая системная воспалительная болезнь, поражающая желудочно-кишечный тракт (ЖКТ) с внекишечными проявлениями и системными иммунологическими нарушениями. Может локализоваться во всех отделах желудочно-кишечного тракта и характеризуется разнообразными кишечными и внекишечными проявлениями,

которые зависят от глубины, протяженности пораженного органа и особенностей иммунных (системных) осложнений. Поражение верхних отделов ЖКТ при данном заболевании представляет собой недостаточно изученную область. Рутинный скрининг показал более высокую распространенность описываемой патологии среди детей по сравнению с взрослыми. У большинства пациентов поражение верхних отделов ЖКТ остается бессимптомным, однако возможны патологические изменения слизистой оболочки, диагностируемые при морфологическом исследовании. В рутинной практике эндоскопическое исследование рекомендуется пациентам с уже имеющимися симптомами поражения. В данном литературном обзоре рассмотрены морфологические изменения в верхних отделах ЖКТ при болезни Крона, являющиеся следствием как основного заболевания, так и побочного действия лекарственных препаратов, используемых при лечении данной патологии.

Ключевые слова: *воспаление, морфология, болезнь Крона*

INTRODUCTION

Crohn's disease (CD) along with ulcerative colitis is one of the predominant clinical entities in the structure of inflammatory bowel disease. At present, CD continues to be considered a chronic disease resulting from a complex interplay of environmental, microbial and genetic factors, despite ongoing research on the etiology and pathogenesis of CD and the progress made in understanding the mechanisms of disease development. Any part of the gastrointestinal (GI) tract can be affected in CD, but the process is usually associated with involvement of the terminal ileum or colon. Cases of CD with isolated or combined involvement of the upper GI tract (esophagus, stomach, and duodenum) are rare and the least studied variants of the disease. This literature review considers upper GI lesions in this pathology.

MORPHOLOGIC CHANGES IN THE ORAL MUCOSA

Oral manifestations of Crohn's disease are both a consequence of primary exposure to the disease, a symptom of a disease of another etiology, or a secondary reaction to drug treatment. The appearance of morphologic changes may also be associated with a secondary manifestation of the intestinal form of Crohn's disease. The results of the study of clinical and morphological features of CD accompanied by oral lesions showed that 33 (38.4%) patients had oral cavity changes, in particular chronic recurrent aphthous stomatitis in 9 (10.46%) patients. In 19 (22.1%) patients, oral symptoms appeared earlier than intestinal manifestations, which is confirmed by the results of histologic examination of the oral mucosa, namely the presence of granulomatous inflammation [1].

Specific mucosal lesions include granulomatous changes that have been noted on histopathologic examination. Although less common than nonspecific lesions, they may occur simultaneously with or even before intestinal symptoms. The oral mucosa is hyperplastic, resembling cobblestone, on which nodular granulomatous swelling is noted. Compacted polyposis fringed lesions of the vestibule and retromolar region are typical. On the mucous membrane of the lips and cheeks, as well as in the retromolar areas are most often found plaques and deep ulcerations of the mucosa with hyperplastic edges, flabby or dense on palpation. The gingiva and alveolar mucosa are swollen, and become granular and hyperplastic with or without ulceration [2]. Swelling of the face, one or both lips and cheek mucosa may also be noted. This condition is unpleasant for patients because it can lead to facial deformity [1]. Granulomatous inflammation can be identified histologically in such lesions. The lips are most commonly affected and are usually painless and solid on palpation. Many patients with swollen lips also have painful vertical fissures in which many microorganisms may be isolated [3].

Non-specific oral lesions in CD include aphthous ulcers, orofacial symptoms predominantly characteristic of young patients, granulomatous cheilitis, and vegetative pyostomatitis [4]. Aphthous ulcers are the most common type of oral lesions, occurring in 20–30% of adult CD patients [2]. The characteristic site of oral lesions is the lips, followed by the mucosa of the cheeks, gums, vestibular and retromolar regions [5]. This phenomenon is a focal inflammation of the oral mucosa in which round ulcers (aphthae or erosions) form. Aphthae are covered with gray or yellowish plaque and cause pain and discomfort. Aphthae with an atypical course are almost indistinguishable from normal aphthae before biopsy. Biopsy material is taken from the upper GI tract

in the presence of clinical signs of the disease, but repeated biopsies in this area are not taken in the absence of clinical and macroscopic manifestations of the pathologic process [6]. It is worth noting that the frequency of aphthous ulcers in inflammatory bowel disease (IBD) is the same as in any other pathology in which they may occur. However, aphthous ulcers occurring in IBD are characterized by a persistent recurrent course [7]. Clinically, the ulcers are small, painful, but benign with a limited erythematous aureola. They may also be part of recurrent aphthous stomatitis or they may be isolated masses [8].

In addition to morphologic changes in the oral cavity, the immunologic profile of cells also changes. According to the results of the study by G.M. Damen et al. the oral cavity cells of CD patients were more immunologically active. Thus, buccal epithelial cells showed increased production of CXCL-8, CXCL-9 and CXCL-10. Lipopolysaccharide-stimulated dendritic cells originating from monocytes produced CXCL-8 [9, 10].

ESOPHAGEAL MORPHOLOGICAL CHANGES

Currently, the likelihood of esophageal involvement in Crohn's disease is considered unlikely. The prevalence of esophageal CD in adults, according to different data, varies from 1.2 to 1.8% and from 3.3 to 6.8%. In children the incidence ranges from 25.8 to 41.5% and from 7.6 to 17.6% [11]. However, histologic evidence of esophageal involvement was found in 54% of pediatric patients with CD: 11% were in association with esophagitis, 33% were in association with chronic inflammation, and 4% were in association with reflux esophagitis, according to S.P. Castellaneta et al. [12].

The diagnosis of the Crohn's disease of the esophagus is difficult to make, as the histologic features of this disease are usually nonspecific and it may present as erosive-ulcerative esophagitis, esophageal stricture or esophageal fistula, which occur in a number of other pathologies. According to K.M. De Felice et al. the most common sites of esophageal involvement were mid (29%), distal (29%), diffuse esophagitis also occurred in 21% of cases. At the time of endoscopic examination, superficial ulceration (58%), erythema and/or erosions (50%), deep ulceration (13%) and pseudopolyps (4%) were the most common findings on the background of hyperemia of the esophageal mucosa. According to De Felice et al. study, the most common localizations of esophageal lesions are middle and distal esophageal lesions — 29%, mid-distal lesions — 17%, diffuse lesions — 21%, proximal lesions — 4% [11].

The most common esophageal lesion in Crohn's disease is lymphocytic esophagitis. Lymphocytic esophagitis (LE) is histologically characterized by marked esophageal lymphocytosis with the absence or presence of only rare intraepithelial granulocytes. At the initial stage of the disease, macrophage and lymphoid infiltration is found only in the submucosal layer, then the pathologic process covers all layers of the digestive tube, incomplete or sarcoid-like granulomas may be found. At the next stage, ulcers occur, extending deep into the serosa until the formation of fistulas. According to a study by Don R. Ebach, the histologic diagnosis of LE is associated with pediatric CD and was found in 28% of CD patients. Esophagitis with granulomas was observed in 10% of CD patients studied [13]. Upon histologic examination, "wavy cells," which are dense intraepithelial lymphocytes, nonspecific for CD, characteristic of both celiac disease and reflux esophagitis, may also be found. The development of eosinophilic esophagitis is possible. It can be distinguished from esophagitis associated with Crohn's disease only by the pathologic Th1-type reaction typical of CD, in contrast to the Th2-type reaction in eosinophilic esophagitis [14].

MORPHOLOGIC CHANGES IN THE MUCOSA OF THE STOMACH AND THE DUODENUM

Gastric and duodenal involvement in CD is rarely clinically evident, but endoscopic examination of the upper GI tract is useful in the presence of distal involvement. Gastroduodenal lesions may present symptoms that imitate peptic ulcer disease, such as pain in the epigastric region, nausea/vomiting and abdominal bloating, and subfebrile body temperature. In pediatric practice, gastritis or duodenitis in CD is often asymptomatic and is usually diagnosed during routine endoscopy. It may manifest as mucosal hyperemia (erythematous gastroduodenitis), erosions or ulcers, fistula formation, stricture, or a combination of these.

The most common clinical picture is permanent involvement of the antral, gatekeeper and

proximal duodenum, affecting up to 60% of patients with duodenal CD [15]. Men and women are equally affected, with a ratio of 1.2:1. Granulomas are found both in abnormal macroscopic structure of the gastric and duodenal mucosa and in its normal structure. Focal acute (neutrophilic) and chronic (lymphocytic) inflammation is often observed [16]. The gastroduodenal mucosa often has focal subepithelial infiltration of macrophages throughout the intrinsic lamina of the mucosa. K. Yao et al. found that in duodenum and stomach, the incidence of macrophage aggregates throughout the intrinsic mucosal lamina was higher than in granulomatous lesions. No macrophage aggregates or granulomas were found in patients with ulcerative colitis. Macrophage infiltration of the intrinsic lamina of the gastroduodenal mucosa was observed in patients with diagnosed Crohn's disease. Researchers suggest that subepithelial accumulations of *lamina propria* macrophages in the absence of signs of inflammation may be one of the minute histologic changes leading to mucosal damage characteristic of CD [17]. The presence of granulomas, superficial intraepithelial accumulations of neutrophils, and infiltration of the intrinsic lamina propria by neutrophilic granulocytes were more frequently observed in *H. pylori* negative patients [18].

CONCLUSION

An increase in the number of people suffering from inflammatory bowel diseases is registered worldwide according to epidemiologic studies. In recent years, there are more and more publications concerning the state of the upper GI tract in these diseases. Unfortunately, the symptomatology at the initial stages of pathology is currently insufficiently studied. There are no views on the evaluation of the place of the lesion in the general picture of the disease, as well as whether it is a complication or refers to the individual course of the disease and does not affect the severity. Further study of this problem will make it possible to diagnose the lesion at early stages, which will significantly improve the prognosis in therapy.

ADDITIONAL INFORMATION

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

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

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 616-056.5-06+616.71-008.1+611.018.4+577.161.2+546.41+616.33-002.2
DOI: 10.56871/CmN-W.2024.79.24.009

VITAMIN D AND BONE METABOLISM IN DISEASES OF THE STOMACH AND DUODENUM

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For citation: Novikova VP, Seits AV. Vitamin D and bone metabolism in diseases of the stomach and duodenum. Children's Medicine of the North-West. 2024;12(3):81–96. DOI: https://doi.org/10.56871/CmN-W.2024.79.24.009

Received: 17.06.2024 **Revised: 22.07.2024** **Accepted: 10.09.2024**

Abstract. The review describes the symptoms of bone damage in diseases of the stomach and duodenum: scoliosis, poor posture, joint diseases, discrepancy between the bone age and the passport age, decreased linear growth rates and recurrent caries. The causes of bone mineral density disorders in chronic gastroduodenitis (CGD) are discussed: prolonged deficiency of micronutrients and protein due to malabsorption, significant deficiency of vitamin D and calcium. The risk factors for the development of mineral dencity in adolescents with CG and CGD, the features of bone metabolism in patients with CG that differ from those in healthy individuals, the effect of Helicobacter pylori (HP) infection on bone tissue condition and the role of vitamin D in the development of H. pylori infection are given. The review shows that currently there are insufficient data characterizing the relationship between the features of the clinical and morphological picture of chronic diseases of the upper digestive tract and Helicobacter pylori infection with the processes of osteosynthesis and remodeling of bone tissue and vitamin D. Further research is needed to develop treatment strategies for Helicobacter pylori infection, gastric neoplasia and gastric cancer.

Keywords: *bone metabolism, vitamin D, calcium, bone mineral density, chronic gastritis, Helicobacter pylori infection*

ВИТАМИН D И КОСТНЫЙ МЕТАБОЛИЗМ ПРИ ЗАБОЛЕВАНИЯХ ЖЕЛУДКА И ДВЕНАДЦАТИПЕРСТНОЙ КИШКИ

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Для цитирования: Новикова В.П., Сейц А.В. Витамин D и костный метаболизм при заболеваниях желудка и двенадцатиперстной кишки // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 81–96. DOI: https://doi.org/10.56871/CmN-W.2024.79.24.009

Поступила: 17.06.2024 **Одобрена: 22.07.2024** **Принята к печати: 10.09.2024**

Резюме. В обзоре описаны симптомы поражения костной системы при заболеваниях желудка и двенадцатиперстной кишки: сколиоз, нарушение осанки, заболевания суставов, несоответствие костного возраста паспортному, снижение показателей линейного роста тела и рецидивирующий кариес. Обсуждаются причины нарушения минеральной плотности костной ткани при хроническом гастродуодените (ХГД): продолжительный дефицит микронутриентов и белка вследствие мальабсорбции, значимый дефицит витамина D и кальция. Приводятся факторы риска развития нарушения минеральной плотности кости у подростков с ХГ и ХГД, особенности костного метаболизма у больных с ХГ, отличающиеся от показателей здоровых лиц, влияние инфицированности пилорическим хеликобактером (НР) на состояние костной ткани и описывается роль витамина D в развитии инфекции *H. pylori*. В обзоре показано, что в настоящее время данных,

которые характеризуют взаимосвязь особенностей клинико-морфологической картины хронических заболеваний верхних отделов пищеварения и хеликобактериоза с процессами остеосинтеза и ремоделирования костной ткани и витамина D, недостаточно. Необходимы дальнейшие исследования для отработки стратегий лечения хеликобактериоза, желудочных неоплазий и рака желудка.

Ключевые слова: *костный метаболизм, витамин D, кальций, минеральная плотность костей, хронический гастрит, хеликобактериоз*

In the works of the last decades it has been noted that in groups of patients of different ages suffering from gastric and duodenal diseases, bone system changes such as scoliosis, posture disorders, joint diseases [1–5], non-compliance of the bone age with the passport age, decreased linear body growth and recurrent dental caries occur with a higher frequency. Most authors report bone mineral density disorders in chronic gastroduodenitis (CGD) [5–9], considering it from the position of prolonged micronutrient and protein deficiency [10–12]. Back in 1991, A.P. Avtsyn et al. wrote: "Every physician, first of all, should be interested in factors that can damage or even destroy the mechanisms of absorption and elimination of micronutrients... The extremely common diagnosis of 'duodenitis', which occurs as often as 'gastritis', from the position of the theory of micronutrients should cause at least a careful attitude. Thus, inflammatory, dystrophic and especially atrophic changes in the duodenal mucosa are inevitably accompanied by disturbances in the absorption of trace elements" [13].

The use of dual-energy X-ray bone densitometry has shown that both children and adults with gastroduodenal diseases have reduced bone mineral density, and the degree of its reduction depends on the duration of the disease and the severity of duodenal lesions [7–10]. G.G. Haustova (2008) revealed that the level of bone mineral density (BMD) in children with CGD is interrelated with the child's age, body length and weight, morphofunctional features of the gastric and intestine mucosa: thickness of the gastric and intestine mucosa, depth of gastric glands, number of secretory granules of the main cells, number of parietal cells of the gastric mucosa, degree of vascularization of the gastric and small intestine mucosa, preservation of structural order and functional activity of the small intestine epithelium [10]. According to O.V. Guzeeva (2012), a decrease in BMD (Z-score <–2SD) in CGD in children is found in 10.6% of cases. The risk factors for the development of BMD disorders in adolescents with CGD are: the presence of an aggravated history of diseases with chronic inflammation (obesity, autoimmune and allergic diseases), the presence of comorbid somatic and allergic diseases, dental enamel disorders and superficial gastritis [5]. In adult patients, osteodensitometric study revealed a high prevalence of BMD reduction in chronic gastritis (CG). Osteopenia was found in 35% of patients in LI-LIV, in 23.3% of controls and in 52% of patients it was found in the proximal femur, while in healthy individuals osteopenia was found in 13.3%. Osteoporosis was found in 23% of patients in LI-LIV and in 13% of patients in the proximal femur, whereas no such BMD changes were found in healthy individuals [9]. Only one study did not describe differences in BMD in patients with CGD and healthy individuals [3].

Most researchers report a significant vitamin D deficiency in patients with gastroduodenal diseases, which increases with the duration of the disease [9, 10]. There is a direct correlation between serum vitamin D levels and the presence of stromal fibrosis and glandular atrophy in the gastric mucosa of adolescents with CG [5]. These results are consistent with the previously obtained data on the relationship between molecular genetic variants of VDR and the degree of inflammatory changes in the gastric mucosa of children with CG [14–16]. It can be explained by the effect of vitamin D on cell proliferation, differentiation and apoptosis [17, 18].

In adult patients with autoimmune atrophic gastritis (AAG) a significant vitamin D deficiency has also been revealed [19–21]. It correlated with the degree of atrophy of the gastric mucosa. The pathogenetic mechanism underlying this association has not been fully elucidated, but it is probably related to a decrease in vitamin D absorption against the background of gastric hypoachlorhydria [21, 22]. Several studies have reported decreased calcium absorption in patients with AAG [18, 19], while another study found no significant differences in calcium absorption in patients with autoimmune gastritis compared to

controls [20]. Since active transcellular absorption of ionized calcium in the duodenum and proximal small intestine represents the most important physiological pathway of calcium absorption and is highly dependent on vitamin D, it seems possible that vitamin D deficiency in patients with AAG explains calcium malabsorption and changes in bone mineralization [20]. In non-autoimmune CG, there is also evidence of decreased serum calcium levels [10]. There are reports of no significant difference between patients with CG and healthy controls [1, 9].

The data on BMD in AAG are controversial. A number of studies have found no significant differences in the incidence of osteoporosis between patients with AAG with vitamin D deficiency and patients with normal levels of vitamin D [20]. At the same time, it has been proven that bone mineral density is reduced in achlorhydria [22–26].

Literature data clearly indicate that not only BMD indices, but also the level of markers of bone metabolism in patients with CG differs from those of healthy individuals [1], and this level depends on the sex of patients and infection with Helicobacter pylori (HP). Thus, adolescents with chronic HP-associated gastritis were significantly more likely than their peers with HP+CG to have bone metabolism disorders in the form of lower levels of osteocalcin and higher values of blood C-terminal telopeptides (CTTP), and boys with HP-associated CG, compared to girls, were characterized by higher serum parathormone levels and lower bone mineral density against the background of a more severe course of CG [27].

It is known from a few studies that helicobacteriosis is often accompanied by a low physical development, disharmonious development, changes in bone remodeling processes and decreased bone mineral density due to impaired nutrient digestion and absorption [18, 29, 30].

It has been revealed that patients with Helicobacter-associated CG also have secondary chronic duodenitis in more than 90% of cases [31–33]. Under the influence of HP, inflammatory morphological changes develop in the duodenal mucosa, leading to a decrease in calcium absorption and its level in the body.

Previous studies have revealed some additional mechanisms of HP influence on calcium metabolism. Thus, the decrease in calcium absorption in Helicobacteriosis is associated with an increase in the absorption of competing with it nickel, the formation of which occurs in the process of destruction of bacterial urease in the stomach [3, 34]. It has been revealed that HP is able to synthesize the enzyme urease, which contains nickel in its structure. Nickel under the action of hydrochloric acid is converted to $NiCl_2$, which is easily absorbed in the stomach. In addition, the increase in the absorption of the trace element may be associated with the presence of nickel transport proteins in HP and the formation of ammonium complexes with NH_3 released during the hydrolysis of urea by bacterial urease [3, 35]. Various undesirable effects associated with toxic and mutagenic effects of this trace element may result from increased nickel intake into the organism during HP infection [11, 13]. It is probable that this effect may result in impaired bone system formation [28].

Some researchers have proposed another mechanism in CG. Thus, it is assumed that in autoimmune gastritis, antibodies to H+K+/ATPase of gastric parietal cells cross-react with a chemically similar enzyme — vacuolar H+/ATPase of osteoclasts [36–38], which is directly involved in the process of bone resorption.

Numerous studies have focused on the relationship between vitamin D deficiency and *H. pylori* infection [39–45]. The results of the published meta-analysis, which studied the relationship between serum vitamin D levels and *H. pylori*, made by M.O. Săsăran et al. in 2023, are presented in Table 1.

Despite the existence of studies that have not confirmed the relationship between helicobacteriosis and vitamin D levels [27, 51, 52, 58, 59], most previous reviews conclude that vitamin D plays an important role in the development of *H. pylori* infection. A large number of studies consider vitamin D deficiency as a risk factor for failure of *H. pylori* eradication [42, 44, 45, 63, 64]. Based on these studies, the therapeutic hypothesis of adding vitamin D_3 to classical eradication regimens emerged and the efficacy of such a regimen was proved [65].

A number of experimental works on mice confirmed the protective role of vitamin D3 in relation to gastric infection with *H. pylori* through upregulation of VDR [66, 67], enhanced activation of the antimicrobial peptide pathway VDR-cathelicidin (CAMP) [66, 67], and restoration of lysosomal degradation through activation of the protein disulfide isomerase A3 (PDIA3) receptor, which promotes calcium release from lysosomes,

ISSN 2221-2582

Table 1. Characteristics of clinical studies assessing the effect of vitamin D deficiency on *H. pylori* infection [39]

Таблица 1. Характеристика клинических исследований, в которых оценивали влияние дефицита витамина D на инфекцию *H. pylori* [39]

Автор, год / Author, year	Тип исследования / Type of study	Исследуемые группы / Study groups	Метод обнаружения *H. pylori* / Method of detection of *H. pylori*	Основной результат / Main result
Habbash et al., 2022 [45]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	200 взрослых пациентов / 200 adult patients: • 111 *H. pylori* положительных пациентов / 111 *H. pylori* positive patients; • 89 *H. pylori* отрицательных пациентов / 89 *H. pylori* negative patients	• Микроскопически 51% обследованных / Microscopic 51% of those examined • Дыхательный уреазный тест у 35,5% / Urease breath test in 35.5% • Оба метода у 13,5% / Both methods in 13.5%	Значительно более высокая распространенность инфекции *H. pylori* среди участников с дефицитом витамина D / Significantly higher prevalence of *H. pylori* infection among participants with vitamin D deficiency
Mut Surmeli et al., 2019 [43]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	254 взрослых пациента / 254 adult patients: • 43 *H. pylori* положительных пациента / 43 *H. pylori* positive patients; • 211 *H. pylori* отрицательных пациентов / 211 *H. pylori* negative patients	Гистологический метод / Histological method	Медиана уровня витамина D в сыворотке крови была значительно ниже в группе *H. pylori* положительных по сравнению с *H. pylori* отрицательных пациентов. Дефицит витамина D был значительно более частым в *H. pylori* положительной группе. Наблюдалась обратная линейная зависимость между сывороточным уровнем витамина D и положительной реакцией на *H. pylori* / The median serum vitamin D level was significantly lower in the *H. pylori* positive group compared to the *H. pylori* negative patients. Vitamin D deficiency was significantly more common in the *H. pylori* positive group. An inverse linear relationship was observed between serum vitamin D level and *H. pylori* positivity
Assaad et al., 2018 [46]	Кросс-секционное исследование / Cross-sectional study	294 взрослых пациента / 294 adult patients: • 154 *H. pylori* положительных пациента / 154 *H. pylori* positive patients; • 140 *H. pylori* отрицательных пациентов / 140 *H. pylori* negative patients	Гистологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	Значимо более высокая распространенность уровня витамина D в сыворотке крови <20 нг/мл среди исследуемой группы *H. pylori* / Significantly higher prevalence of serum vitamin D levels <20 ng/mL among the *H. pylori* study group
Bashir et al., 2016 [47]	Интервенционное моноцентровое открытое пилотное исследование / Interventional monocentric open-label pilot study	15 здоровых взрослых / 15 healthy adults: • 3 пациента с диагнозом *H. pylori* / 3 patients diagnosed with *H. pylori*	Гистологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	В подгруппе, у которой была диагностирована инфекция *H. pylori*, 8-недельный режим приема добавок с высоким пероральным содержанием витамина D_3 приводил к значительному снижению колонизации слизистой оболочки желудка *H. pylori* / In the subgroup diagnosed with *H. pylori* infection, an 8-week high-dose oral vitamin D_3 supplementation regimen resulted in a significant reduction in gastric mucosal colonization with *H. pylori*

Автор, год / Author, year	Тип исследования / Type of study	Исследуемые группы / Study groups	Метод обнаружения *H. pylori* / Method of detection of *H. pylori*	Основной результат / Main result
Shafrir et al., 2021 [44]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	150 483 взрослых пациента / 150,483 adult patients: • 75 640 *H. pylori* положительных пациентов / 75,640 *H. pylori* positive patients; • 74 843 *H. pylori* отрицательных пациента / 74,843 H. pylori negative patients	Дыхательный уреазный тест в 99% случаев / Urea breath test in 99% of cases Анализ кала на антиген в остальных случаях / Stool antigen test in the rest	Средние уровни витамина D в сыворотке крови были значительно выше в отрицательной группе *H. pylori*. Наблюдалась обратная линейная зависимость между сывороточным уровнем витамина D и положительной реакцией на *H. pylori*. Более высокая распространенность *H. pylori* среди лиц со значениями витамина D <20 нг/мл / Mean serum vitamin D levels were significantly higher in the *H. pylori* negative group An inverse linear relationship was observed between serum vitamin D levels and *H. pylori* positivity Higher prevalence of *H. pylori* among individuals with vitamin D values < 20 ng/mL
Han et al., 2019, [48]	Многоцентровое обсервационное и проспективное когортное исследование / A multi-center observational and prospective cohort study	672 взрослых пациента / 672 adult patients: • 415 *H. pylori* положительных пациента / 415 *H. pylori* positive patients; • 257 *H. pylori* отрицательных пациентов / 257 *H. pylori* negative patients	Дыхательный тест на мочевину / Urea breath test	Значительно более низкие уровни витамина D в сыворотке крови в группе *H. pylori* / Significantly lower serum vitamin D levels in the *H. pylori* group
Assaad et al., 2019 [49]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	460 взрослых пациентов / 460 adult patients: • 225 *H. pylori* положительных пациентов / 225 H. pylori positive patients; • 235 *H. pylori* отрицательных пациентов / 235 *H. pylori* negative patients	Гистологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	Значимо более высокая распространенность недостаточности витамина D среди исследовательской группы *H. pylori*. Обнаружена обратная зависимость между двумя однонуклеотидными полиморфизмами TLR4 и уровнями витамина D / Significantly higher prevalence of vitamin D deficiency among the study group *H. pylori*. Inverse association found between two TLR4 single nucleotide polymorphisms and vitamin D levels
Mohammed et al., 2021 [50]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	100 здоровых женщин с ожирением / 100 healthy obese women: • пациенты 1–3 группы с недостаточностью витамина D + группа 2–10 пациентов с недостаточностью витамина D / group 1–3 vitamin D deficient patients + group 2–10 vitamin D-deficient patients H. pylori; • *H. pylori* отрицательная — группа 3–13 пациентов с дефицитом витамина D / Group 3–13 vitamin D-deficient patients *H. pylori*+;	Обнаружение специфических сывороточных антител (IgM и IgG), направленных против *H. pylori* / Detection of specific serum antibodies (IgM and IgG) directed against *H. pylori*	Различия в показателях положительного результата на антитела к *H. pylori* в сыворотке крови наблюдались только между группами 3 и 4, в которых наблюдался дефицит витамина D / Differences in serum *H. pylori* antibody positivity were observed only between Groups 3 and 4, which had vitamin D deficiency

ISSN 2221-2582

ISSN 2221-2582

Continuation of the table 1 / Продолжение табл. 1

Автор, год / Author, year	Тип исследования / Type of study	Исследуемые группы / Study groups	Метод обнаружения *H. pylori* / Method of detection of *H. pylori*	Основной результат / Main result
		• *H. pylori* положительная — группа 4–74 пациентов с дефицитом витамина D *H. pylori*– /group 4–74 vitamin D-deficient patients *H. pylori*–		
Chen et al., 2016 [51]	Проспективное исследование на базе сообщества / A community-based prospective study	2113 взрослых пациентов / 2113 adult patients: • 557 пациентов с метаболическим синдромом / 557 patients with metabolic syndrome; • 1556 пациентов без метаболического синдрома / 1556 patients without metabolic syndrome	Дыхательный уреазный тест / Urea breath test	Уровни витамина D были одинаковыми среди включенной популяции, независимо от инфекционного статуса *H. pylori*. Субъекты, инфицированные *H. pylori* и с дефицитом витамина D, были наиболее восприимчивы к развитию метаболического синдрома / Vitamin D levels were similar among the included population, regardless of infection status *H. pylori*. Subjects infected with *H. pylori* and with vitamin D deficiency were most susceptible to developing metabolic syndrome
Gerig et al., 2013 [52]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	404 взрослых пациента с ожирением, перенесших бариатрическую операцию / 404 obese adult patients undergoing bariatric surgery: • 85 *H. pylori* положительных пациентов / 85 *H. pylori* positive patients; • 319 *H. pylori* отрицательных пациентов / 319 *H. pylori* negative patients	Гистопатологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	Не было существенных различий в уровнях витамина D между двумя исследуемыми группами / There were no significant differences in vitamin D levels between the two study groups
Mihalache et al., 2016 [53]	Перекрестное обсервационное исследование / Cross-sectional, observational study	93 взрослых пациента с ожирением / 93 obese adults: • 47 пациентов с положительным результатом на *H. pylori* / 47 patients positive for *H. pylori*; • 46 пациентов с отрицательным результатом на *H. pylori* / 46 patients negative for *H. pylori*	Гистопатологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	Несколько более высокие средние уровни витамина D в сыворотке крови были обнаружены у пациентов, инфицированных инфекцией *H. pylori*, но эта разница не достигла статистической значимости / Slightly higher mean serum vitamin D levels were found in patients infected with *H. pylori*, but this difference did not reach statistical significance
Mirza et al., 2022 [54]	Проспективное исследование «случай–контроль» / Prospective case–control study	800 взрослых субъектов / 800 adult subjects: • 400 пациентов с лихорадкой денге (*H. pylori* положительный и *H. pylori* отрицательный) / 400 dengue patients (*H. pylori* positive and *H. pylori* negative)	Дыхательный уреазный тест / Urea breath test	У пациентов с лихорадкой денге и коинфекцией, вызванной *H. pylori*, уровни витамина D были значительно ниже, чем у здоровой контрольной группы, у которой была диагностирована инфекция *H. pylori*. Пациенты с лихорадкой денге, коинфицированные *H. pylori*, имели более высокую вероятность дефицита витамина D, чем те, у кого бактериальная инфекция не была обнаружена /

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Автор, год / Author, year	Тип исследования / Type of study	Исследуемые группы / Study groups	Метод обнаружения *H. pylori* / Method of detection of *H. pylori*	Основной результат / Main result
		• 400 здоровых людей из контрольной группы (*H. pylori* положительный и *H. pylori* отрицательный) / 400 healthy controls (*H. pylori* positive and *H. pylori* negative)		Patients with dengue and *H. pylori* coinfection had significantly lower vitamin D levels than healthy controls diagnosed with *H. pylori* infection Dengue patients coinfected with *H. pylori* were more likely to be vitamin D deficient than those without bacterial infection
Nasri et al., 2007 [55]	Кросс-секционное исследование / Cross-sectional study	36 взрослых пациентов с терминальной стадией почечной недостаточности, находящихся на гемодиализе / 36 adult patients with end-stage renal disease undergoing hemodialysis	Обнаружение специфических сывороточных антител (IgG), направленных против *H. pylori* / Detection of specific serum antibodies (IgG) directed against *H. pylori*	Значимая положительная связь между уровнем витамина D в сыворотке крови и титром специфических антител IgG к *H. pylori* / Significant positive association between serum vitamin D level and titer of specific IgG antibodies to *H. pylori*
Bener et al., 2020 [56]	Проспективное исследование «случай–контроль» / Prospective case–control study	1058 взрослых субъектов / 1058 adult subjects: • 529 пациентов с сахарным диабетом 2-го типа / 529 patients with type 2 diabetes; • 529 здоровых людей соответствующего возраста / 529 healthy age-matched controls	Обнаружение специфических сывороточных антител (IgA и IgG), направленных против *H. pylori* / Detection of specific serum antibodies (IgA and IgG) directed against *H. pylori*	Значительно более низкие уровни витамина D в сыворотке крови у пациентов с сахарным диабетом 2-го типа и серопозитивностью IgA/IgG по сравнению с контрольной группой с положительными сывороточными антителами / Significantly lower serum vitamin D levels in patients with type 2 diabetes and IgA/IgG seropositivity compared to controls with positive serum antibodies
Zawada et al., 2023 [57]	Кросс-секционное исследование / Cross-sectional study	103 взрослых пациента с сахарным диабетом 1-го типа / 103 adult patients with type 1 diabetes mellitus: • 31 *H. pylori* положительный пациент / 31 *H. pylori* positive patients; • 72 *H. pylori* отрицательных пациента / 72 *H. pylori* negative patients	Анализ кала на антиген *H. pylori* / Stool testing for *H. pylori* antigen	Значительно более низкие уровни витамина D в сыворотке крови у пациентов с инфекцией *H. pylori*. Значимая связь между более низкими уровнями витамина D в сыворотке крови и положительными тестами на антиген *H. pylori* в стуле / Significantly lower serum vitamin D levels in patients with *H. pylori* infection. Significant association between lower serum vitamin D levels and positive stool tests for *H. pylori* antigen
Agin et al., 2021 [58]	Проспективное исследование «случай–контроль» / Prospective case–control study	291 ребенок, которым была выполнена эндоскопия верхних отделов пищеварительной системы: 38 пациентов с язвенной болезнью желудка и 253 пациента с болезнью двенадцатиперстной кишки / 291 children who underwent upper gastrointestinal endoscopy: 38 patients with gastric ulcer and 253 patients with duodenal ulcer	Гистологическое исследование биопсийных образцов желудка / Histological examination of gastric biopsy samples	Значимая связь между более низкими уровнями витамина D в сыворотке крови и наличием язвенной болезни. Отсутствие изменений в уровнях витамина D в связи с инфекцией *H. pylori* / Significant association between lower serum vitamin D levels and the presence of peptic ulcer. No change in vitamin D levels associated with *H. pylori* infection

Ending of the table 1 / Окончание табл. 1

Автор, год / Author, year	Тип исследования / Type of study	Исследуемые группы / Study groups	Метод обнаружения *H. pylori* / Method of detection of *H. pylori*	Основной результат / Main result
Urganci et al., 2020 [59]	Проспективное кросс-секционное исследование / Prospective cross-sectional study	100 детей с хроническим гастритом / 100 children with chronic gastritis: • 72 *H. pylori* положительных пациента / 72 *H. pylori* positive patients • 28 *H. pylori* отрицательных пациентов / 28 *H. pylori* negative patients	По крайней мере два из трех обследований / At least two of three examinations: гистологическое исследование образцов биопсии желудка / histological examination of gastric biopsy samples; бактериологическое исследование образцов биопсии желудка / bacteriological examination of gastric biopsy samples; уреазный экспресс-тест с биоптатом слизистой оболочки желудка / rapid urease test with gastric mucosa biopsy serum	Уровни витамина D в сыворотке крови были одинаковыми между двумя исследуемыми группами / Vitamin D levels were similar between the two study groups
Gao et al., 2020 [60]	Ретроспективное кросс-секционное исследование / Retrospective cross-sectional study	6896 внешне здоровых младенцев и детей ясельного возраста / 6896 apparently healthy infants and toddlers: • 2113 Серопозитивные лица по *H. pylori* / 2113 *H. pylori* seropositive individuals • 4783 Серонегативные лица по *H. pylori* / 4783 *H. pylori* seronegative individuals	Обнаружение специфических сывороточных антител (IgG), направленных против *H. pylori* / Detection of specific serum antibodies (IgG) directed against *H. pylori*	Значительно более высокая распространенность дефицита витамина D среди серопозитивных детей, инфицированных *H. pylori* / Significantly higher prevalence of vitamin D deficiency among *H. pylori* seropositive children

lysosomal acidification and, consequently, elimination of *H. pylori* through the autolysosomal pathway [68]. Synthetic production of vitamin D-derived indene compounds has been shown to result in selective antibacterial effect against *H. pylori* [69, 70]. In particular, vitamin D products, such as vitamin D3 product 1 (VDP1), delay effects against *H. pylori* by inducing collapse of the cell membrane structure of bacteria [71]. The inhibitory effect of 1α,25-dihydroxyvitamin D_3 on *H. pylori*-induced apoptosis of gastric epithelial cells was proved [72].

Gastric mucosal cells from patients infected with *H. pylori* showed a significant increase in VDR expression compared to the healthy control group [73]. A significant correlation was also found between FokI and ApaI polymorphisms of the *VDR* gene and BsmI genotypes of the *VDR* gene and *H. pylori* infection [74]. The other three polymorphisms studied, namely FokI, ApaI and TaqI, showed no significant variations in genotype distribution between the two groups studied [75].

Several studies have shown significantly lower levels of 25-OHvitD in patients with gastric neuroendocrine neoplasms (NEN) compared to patients without gastric NEN. The pathogenetic mechanism leading to this association has been attributed to the pleiotropic effects of vitamin D [47, 51, 76, 77]. In the last few years, a number of studies have also focused on the antitumor properties of vitamin D in various solid neoplasms [48, 51, 74]. Tumor suppressor protein 3 (VDUP1) was found to increase the regulation of vitamin D_1 (VDUP67), which has been shown to be protective against gastric carcinogenesis [3].

Nevertheless, there is currently insufficient data that characterize the relationship between the clinical and morphological features of chronic upper digestive diseases and helicobacteriosis and the processes of osteosynthesis and bone remodeling and vitamin D. Further studies are needed in order to refine strategies for the treatment of helicobacteriosis, gastric neoplasia and gastric cancer.

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 616-039.75+616.321-008.17+616.33-089.86
DOI: 10.56871/CmN-W.2024.56.77.010

A THREE-LEVEL PALLIATIVE CARE SYSTEM FOR PATIENTS WITH DYSPHAGIA

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For citation: Ivanov DO, Orel VI, Gavshchuk MV. A three-level palliative care system for patients with dysphagia. Children's Medicine of the North-West. 2024;12(3):97–101. DOI: https://doi.org/10.56871/CmN-W.2024.56.77.010

Received: 03.06.2024 **Revised: 04.07.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* Humanism is the foundation of modern civilization and dictates the need to provide palliative care to the terminally ill patients. A separate problem is the organization of enteral nutrition of palliative patients through gastrostomy, which is important for patients of all age groups. *The aim of the work* is to optimize the palliative care for patients with dysphagia. *Materials and methods.* Scientific methods of analysis, synthesis, analogy, deduction and induction were used to develop a palliative care system for patients with dysphagia. At the same time, data from the content analysis of documents regulating the provision of palliative care to patients with dysphagia and the materials of previous studies are taken into account. *Results.* A system has been developed for the palliative care for patients with dysphagia organization, which distinguishes three levels: the outpatient level of palliative care, inpatient hospice and the level of a specialized surgical hospital with clear routing of patients and the definition of appropriate measures for each level. *Conclusions.* The developed three-level palliative care system for patients with dysphagia makes it possible to improve the quality of care and use Fast-track surgery approaches for this group of patients.

Keywords: *palliative care, routing, dysphagia, gastrostomy, Fast-track surgery*

ТРЕХУРОВНЕВАЯ СИСТЕМА ОКАЗАНИЯ ПАЛЛИАТИВНОЙ ПОМОЩИ БОЛЬНЫМ С ДИСФАГИЕЙ

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Для цитирования: Иванов Д.О., Орел В.И., Гавщук М.В. Трехуровневая система оказания паллиативной помощи больным с дисфагией // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 97–101. DOI: https://doi.org/10.56871/CmN-W.2024.56.77.010

Поступила: 03.06.2024 **Одобрена: 04.07.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение.* Гуманизм является основой современной цивилизации и диктует необходимость оказывать паллиативную помощь неизлечимым больным. Отдельную проблему представляет организация энтерального питания паллиативных больных через гастростому, что актуально у пациентов всех возрастных групп. *Цель работы* — оптимизировать оказание паллиативной помощи больным с дисфагией. *Материалы и методы.* Для разработки системы оказания паллиативной помощи больным с дисфагией использованы научные методы анализа, синтеза, аналогии, дедукции и индукции. При этом учтены данные контент-анализа документов, регламентирующих оказание паллиативной медицинской помощи больным с дисфагией, и и материалы проведенных ранее исследований. *Результаты*. Разработана система организации паллиативной помощи больным с дисфагией, выделяющая три уровня: амбулаторный уровень оказания паллиативной медицинской помощи, стационарный хоспис и уровень специализированного

хирургического стационара с четкой маршрутизацией пациентов и определением соответствующих каждому уровню мероприятий. *Выводы.* Разработанная трехуровневая система оказания паллиативной помощи больным с дисфагией позволяет повысить качество оказываемой помощи и использовать подходы Fast-track хирургии для этой группы больных.

Ключевые слова: *паллиативная помощь, маршрутизация, дисфагия, гастростомия, Fast-track хирургия*

INTRODUCTION

Humanism is the basis of a modern civilization. It dictates the importance of providing palliative care to terminally ill patients. The estimated need for palliative care in the Russian Federation in 2021 was about 1 million 200 thousand people, including 92 thousand children [1].

A special problem is the organization of enteral nutrition of palliative patients through a gastrostomy, which is relevant in patients of all age groups [2–4]. The formation of a nutritional fistula is a surgical operation which performed as part of specialized medical care in the profile of "surgery". Prolonged stay of a palliative patient in a specialized surgical bed is economically inexpedient, and the peculiarities of this group of patients, expected complications and lethal outcomes negatively affect the psycho-emotional state and satisfaction with the quality of care provided to other patients of the unit. This necessitates the application of Fast-track surgery approaches [5] aimed at reducing the duration of treatment in a surgical hospital and the period of habilitation of patients with dysphagia. Of particular interest is the possibility of performing necessary surgical interventions in the conditions of an emergency unit [6, 7] with subsequent transfer to the hospice for palliative care.

Previous studies [8, 9] demonstrated the lack of a unified system of palliative care for patients with dysphagia and related continuity disorders. In addition, the formation of a feeding fistula is required in patients with various diseases. The surgeon, who is not a specialist in the disease, does not have the legal and moral right to make predictions about the patient's life expectancy, assess the feasibility of surgical intervention and refuse palliative surgery.

AIM

The aim of the work is to optimize the palliative care of patients with dysphagia

MATERIALS AND METHODS

Scientific methods of analysis, synthesis, analogy, deduction and induction were used to achieve the aim. The data of content analysis of documents regulating the provision of palliative care for patients with dysphagia and the results of previous studies were taken into account [4, 6–9].

RESULTS

It is reasonable to use Fast-track surgery approaches for this group of patients to create a three-level system of palliative care organization for patients with dysphagia, based on the level of institutions providing palliative care (Fig. 1). This approach is successfully used in the organization of the system of emergency, including specialized, medical care [10, 11] and can be applied to the organization of palliative care.

The first level is outpatient, within the framework of which palliative care is provided by a doctor on the profile of the main disease or specialized palliative care. The severity of the patients' condition makes it difficult to perform diagnostic measures and preoperative preparation on an outpatient basis. In case of dysphagia development, it is suggested to refer the patient to the next level.

The second level is a hospice with 24-hour beds, where the patient receives specialized palliative medical care. It may include clarification of prognosis and indications for palliative surgical intervention, necessary preoperative preparation of the patient. If the patient is diagnosed grade III–IV dysphagia, but the expected duration of dysphagia or life expectancy is less than one month, surgical intervention is not indicated.

The third level is a surgical or multidisciplinary hospital, where the patient should be admitted from hospice after verification of the indications for surgery, taking into account the available prognosis and preoperative preparation. After the surgical procedure is performed and there are no postoperative complications within the Fast-track approach, the patient is transferred to a 24-hour hospice for further treatment. In some cases, transfer to outpatient care is possible.

Before surgery, at the first and second levels, the patient should be consulted by a dietician. Furthermore, the patient should be provided with appropriate nutrition in accordance with Articles 78 and 79 of St. Petersburg Law N 728–132 of 22.11.2011 (revised on 30.06.2022) "The Social Code

Fig. 1. Scheme of a three-level palliative care system for patients with dysphagia

Рис. 1. Схема трехуровневой системы оказания паллиативной помощи больным с дисфагией

ISSN 2221-2582
Children's Medicine of the North-West
2024 / Vol. 12 № 3

of St. Petersburg" and the order of the Committee for Economic Policy and Strategic Planning of the Government of St. Petersburg "On approval of standards for financing the budget expenditures of St. Petersburg for the provision of formula for enteral nutrition, drugs for parenteral nutrition, consumables and equipment for clinical enteral or parenteral nutrition at home for the current year".

Thus, the duration of expensive inpatient treatment in the surgical profile is minimized, and the continuity and quality of care for patients with dysphagia is improved.

The developed system of enteral nutrition organization for palliative patients was successfully tested from 2021 to 2023 as a pilot project with the participation of the rehabilitation department of stoma patients of the State Budgetary Institution "City Clinical Oncological Dispensary", hospice of St. Petersburg State Budgetary Institution "City Hospital N 14", St. Petersburg State Budgetary Institution "City Hospital N 26" and hospice of St. Petersburg State Budgetary Institution "City Polyclinic N 91" [12]. The algorithm was applied in 17 patients of the 4th clinical group with dysphagia of tumor genesis aged from 37 to 84 years. The average age was 61.4±14.01 years. Application of the algorithm allowed to minimize the duration of the hospital period, to increase the efficiency of training the patient and relatives in nursing measures, to optimize the habilitation process and to minimize the risk of complications caused by nursing defects. The severity of the condition and expected mortality in this group of patients does not allow the use of time indicators as criteria of effectiveness. The expediency of the algorithm application is confirmed by providing all patients with enteral nutrition, low frequency of complications due to care defects, which were observed only in 2 (11.8%) cases and were managed by conservative measures. The proposed algorithm was successfully implemented in pilot mode with a limited number of participants and can be extrapolated on a larger scale.

CONCLUSION

The developed three-level system of palliative care for patients with dysphagia specifies routing and measures corresponding to each level, which allows to improve the quality of care and use Fast-track surgery approaches for this group of patients.

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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 ISSN 2221-2582

UDC 616-084-053.37+614.812+340.115.4
DOI: 10.56871/CmN-W.2024.90.94.011

IMPROVING THE PROCESS OF PREVENTIVE MEDICAL EXAMINATION OF CHILDREN USING LEAN TECHNOLOGIES

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For citation: Orel VI, Smirnova VI, Gureva NA, Surenkova IN, Kim AV, Sereda VM, Sharafutdinova LL, Orel VV, Buldakova TI, Kulev AG, Ushkats AK, Roslova ZA, Kakanov AM, Razgulyaeva DN. Improving the process of preventive medical examination of children using lean technologies. Children's Medicine of the North-West. 2024;12(3):102–109. DOI: https://doi.org/10.56871/CmN-W.2024.90.94.011

Received: 21.05.2024 **Revised: 08.07.2024** **Accepted: 10.09.2024**

Abstract. The article presents ways to improve the process of preventive medical examinations of children aged 12 months. The existing system of preventive medical examination of children did not meet the child's priorities for high-quality and affordable medical care, as it required a lot of time and unnecessary movements on the part of the patient. The basic tools of lean manufacturing (mapping, timekeeping, spaghetti diagram), as well as the sociological method were used to analyze the root causes. The use of lean technologies during the reorganization of the process of preventive medical examination of children aged 12 months has reduced the burden, first of all, on parents, as well as on the medical organization for the implementation of this process. The number of visits by the patient to the polyclinic for preventive medical examination decreased by 6 times, the time spent by the patient for preventive medical examination decreased by 8.3 times, convenient schedule of doctors' appointments and rational navigation and routing of patients led to the disappearance of queues at the offices, the production efficiency of the team of medical workers involved in preventive medical examinations increased, which was expressed in a 2 fold increase in admitted patients, from 16 to 32 people per shift, as a result, the coverage of children aged 12 months with preventive medical examinations in the month they reach this age was 100%. According to the data of a sociological survey of parents after the introduced transformations, their level of satisfaction with the process of passing a preventive medical examination of a child is 100%. The selected lean manufacturing technologies have proven their effectiveness in improving the process of preventive medical examination of children in a children's polyclinic.

Keywords: *lean manufacturing tools, preventive medical examination, process improvement, accessibility and quality of medical care*

СОВЕРШЕНСТВОВАНИЕ ПРОЦЕССА ПРОФИЛАКТИЧЕСКОГО МЕДИЦИНСКОГО ОСМОТРА ДЕТЕЙ С ПРИМЕНЕНИЕМ БЕРЕЖЛИВЫХ ТЕХНОЛОГИЙ

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Для цитирования: Орел В.И., Смирнова В.И., Гурьева Н.А., Суренкова И.Н., Ким А.В., Середа В.М., Шарафутдинова Л.Л., Орел В.В., Булдакова Т.И., Кулев А.Г., Ушкац А.К., Рослова З.А., Каканов А.М., Разгуляева Д.Н. Совершенствование процесса профилактического медицинского осмотра детей с применением бережливых технологий // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 102–109. DOI: https://doi.org/10.56871/CmN-W.2024.90.94.011

Поступила: 21.05.2024 **Одобрена: 08.07.2024** **Принята к печати: 10.09.2024**

Резюме. В статье представлены пути совершенствования процесса проведения профилактических медицинских осмотров детей в возрасте 12 месяцев. Существовавшая система прохождения профилактического медицинского осмотра детей не отвечала приоритетам ребенка на доступную медицинскую помощь, так как требовала больших временны`х затрат и лишних перемещений со стороны пациента. Для анализа коренных причин были использованы основные инструменты бережливого производства (картирование, хронометраж, диаграмма спагетти), а также социологический метод. Использование бережливых технологий в ходе реорганизации процесса профилактического медицинского осмотра детей в возрасте 12 месяцев позволило снизить нагрузку, в первую очередь, на родителей, а также на медицинскую организацию по реализации данного процесса. Количество посещений пациентом поликлиники для прохождения профилактического медицинского осмотра сократилось в 6 раз, время, затрачиваемое пациентом на прохождение профилактического медицинского осмотра, уменьшилось в 6,8 раза, удобное расписание приема врачей и рациональная навигация и маршрутизация пациентов привели к исчезновению очередей у кабинетов, производственная эффективность бригады медицинских работников, задействованных при проведении профилактических медицинских осмотров, выросла, что выражалось в увеличении принятых пациентов в 2 раза, с 16 до 32 человек в смену, в результате охват детей в возрасте 12 месяцев профилактическими медицинскими осмотрами в месяц достижения ими данного возраста составил 100%. Согласно данным социологического опроса родителей после введенных преобразований, уровень их удовлетворенности процессом прохождения профилактического медицинского осмотра ребенка составил 100%. Выбранные технологии бережливого производства доказали свою эффективность для совершенствования процесса профилактического медицинского осмотра детей в условиях детской поликлиники.

Ключевые слова: *инструменты бережливого производства, профилактический медицинский осмотр, совершенствование процесса, доступность и качество медицинской помощи*

INTRODUCTION

Preserving and strengthening the health of the child population is the main strategic objective of the health care system of the Russian Federation. The state of health of the child population is characterized by demographic processes, the level of physical development, morbidity and disability indicators. At present, there are negative trends in the growth of morbidity and chronic pathologies in children, which determines the need to improve treatment, diagnosis and preventive measures. One of the priority principles of organizing and conducting preventive medical measures among children is the coverage of certain age categories with timely and high-quality medical check-ups in children's polyclinics [8–10]. In accordance with the order of the Ministry of Health of Russia from 10.08.2017 N 514n "On the order of medical check-ups for minors", check-ups are carried out in the established age periods for the purpose of early (timely) detection of pathological conditions, diseases and risk factors for their development, non-medical use of narcotic drugs and psychotropic substances, as well as for the purpose of determining health groups and making recommendations for minors and their parents or other legal representatives [1]. This order expands the program of check-ups for children compared to the one in force before it. Medical organizations perform professional medical check-ups in the scope stipulated by the list of tests stipulated in Order N 514n of the Ministry of Health of the Russian Federation.

All the above-mentioned reasons have shown the necessity to create a certain system of organization of professional medical check-ups.

AIM

To analyze and identify time losses in the process of organizing and performing professional

medical check-ups for children at the age of 12 months.

MATERIALS AND METHODS

The study was conducted within the framework of the regional project "Development of primary health care system" aimed at improving the availability and quality of medical care. On the basis of one of the medical organizations providing primary health care to children ("Children's polyclinic"), a pilot project was implemented to introduce the principles and methods of lean production in the process of "Reducing the time of medical check-ups for children aged 12 months" in order to reduce time losses during preventive medical check-ups and the patient's stay in the medical organization.

The organization and implementation of medical check-ups for children aged 12 months with the use of lean production techniques have been studied. Within the framework of this study, the main tools of lean production [5, 6, 11] (the mapping, timekeeping, spaghetti diagram), as well as the sociological method were used to analyze the root causes.

This study was implemented in four stages. At the first stage, a questionnaire was administered to parents of children who underwent this event, in order to identify problems and assess the organization of medical check-ups. The questionnaire included a number of questions: accessibility of medical care, conditions of stay in the polyclinic, waiting time for examinations, time to undergo a preventive medical examination, awareness of the possibility to undergo it. A total of 221 respondents took part in the questionnaire. The main share of respondents were mothers — 81.0%, grandmothers — 11.8% and fathers — 7.2%.

At the second stage, lean production methods and tools were applied to solve the identified problems within the framework of the questionnaire such as the mapping, timekeeping and spaghetti diagram [5–7, 11].

In the third stage of the study, targets were determined based on the results obtained in the second stage.

In the course of the fourth stage, a map of the target state was built and a set of measures to achieve the target indicators was developed.

RESULTS AND DISCUSSION

The medical organization selected as the base of the study is located in an actively building dormitory district of St. Petersburg. The children's polyclinic is provided with medical equipment necessary for medical activities in accordance with the order of the Ministry of Health of Russia from 07.03.2018 N 92n "On approval of the Regulations on the organization of primary medical and sanitary care for children" [2]. The structure of the children's polyclinic includes the following medical and preventive departments: pediatric, department of organization of medical care for minors in educational organizations, department of specialist doctors, ophthalmology department, department of medical and social assistance, department of functional diagnostics, dental department, department of physiotherapy, manual exercise, hydrotherapy, healthy child department. The children's polyclinic has 18 pediatric districts, and the staffing level of pediatricians is 100%. The children's polyclinic serves 16,244 children according to the district principle, of whom 6.0% are children aged 12 months.

The results of the questionnaire survey conducted within the first stage of the study showed that 35.3% of respondents were fully satisfied with the medical check-up. The share of partially satisfied respondents was 42.1%, the share of dissatisfied respondents was 22.6% (Fig. 1).

Among the partially satisfied and dissatisfied respondents, 54.2% noted that they had to visit a children's polyclinic to see all specialists and tests within the framework of medical check-up more than 5 times, 64.8% experienced difficulties in making appointments with specialists, 26.4% were dissatisfied with the conditions of stay in the medical organization (lack of seating in the waiting area, having to wait in line with older children). 67.6% of respondents spent more than 20 minutes waiting for appointments in front of doctors' cabinets and 72.2% took a month to do their medical checkup.

In order to solve the problems identified in the questionnaire, to determine the procedures and regulations for the organization of the medical check-ups in the second stage, complete information about all operations of the process was collected and the current state was assessed using lean production tools: the mapping, timekeeping and spaghetti diagram [5–7, 11]. Based on the analysis of the duration and sequence of all the operations of the process using timekeeping, the patient's itinerary and their time cost for investigations in the professional medical check-ups were studied. The cycle time of the whole process and the tact time of each operation were calculated [3–6, 9, 11].

The spaghetti diagram made it possible to see the unnecessary movements of the patient around the pediatric polyclinic and to identify the intersection of flows during medical check-ups.

Based on the results of the conducted timekeeping and mapping of the current state, the following were identified: intersection of different patient flows in front of doctors' cabinets, at the reception (for vaccinations, for preventive medical examinations, to obtain health certificates); a large number of visits to the children's clinic (undergoing specialist doctors, functional and laboratory tests on different days) — up to 6 visits; excessive movement around the medical organization (cabinets of doctors and cabinets for examination were located on the different floors of the children's clinic); long waiting time in the queue (up to 20 minutes); the process takes 9 hours 10 minutes; the lack of routing during professional medical check-ups (parents independently chose the traffic patterns for visiting a specialist doctor); long time for processing medical documentation; low throughput per shift — no more than 16 people (Fig. 2).

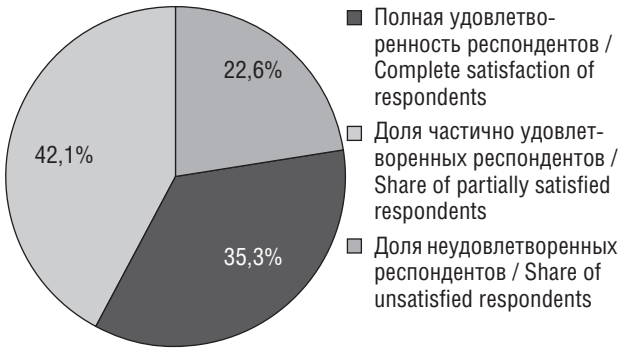

Fig. 1. Indicators of satisfaction of parents by the process of preventive medical examination of their children (%)

Рис. 1. Показатели удовлетворенности родителей проведением профилактического медицинского осмотра ребенка (%)

At the third stage of the study, taking into account the mapping and the identified problems in the process, target indicators for optimizing the medical check-ups of children aged 12 months were determined (Table 1).

To eliminate the problems and achieve the target indicators, a target state map was constructed with the estimated time of passing the preventive medical check-up of a child aged 12 months (Fig. 3).

Taking into account the identified problem areas, a set of measures was developed to improve the process of medical check-ups:

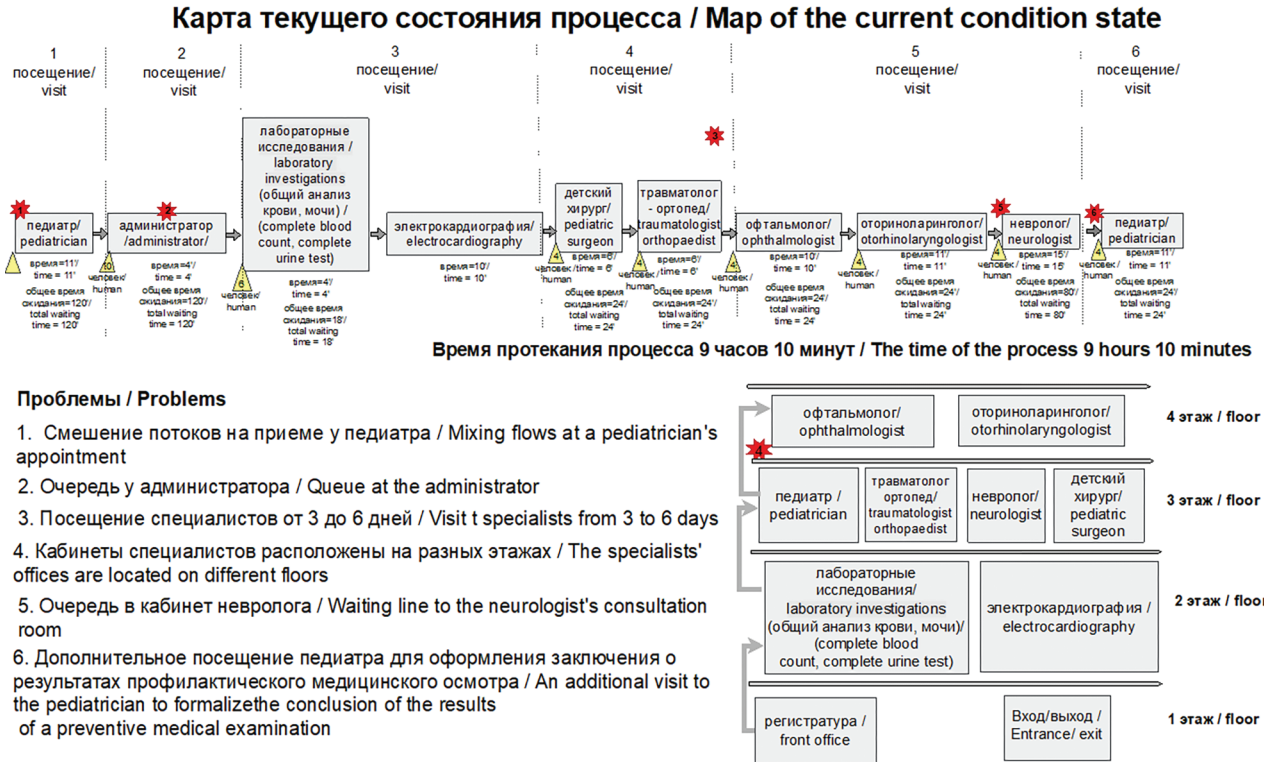

Fig. 2. Process map "Reducing the time for preventive medical examination of children aged 12 months (current condition)"

Рис. 2. Карта процесса «Сокращение времени прохождения профилактического медицинского осмотра детей в возрасте 12 месяцев (текущее состояние)»

Table 1. Target indicators of the process "Reduction of time for preventive medical examination of children at the age of 12 months"

Таблица 1. Целевые показатели процесса «Сокращение времени прохождения профилактического медицинского осмотра детей в возрасте 12 месяцев»

Наименование цели (ед. изм.) / Target name (unit)	Текущий показатель / Current indicator	Целевой показатель / Target indicator
Сокращение количества посещений медицинской организации при прохождении профилактического медицинского осмотра / Reduction of number of visits to the medical organization for preventive medical examination	6 посещений / 6 visits	1 посещение /1 visit
Сокращение времени пребывания в медицинской организации при прохождении профилактического медицинского осмотра / Reduction of the time period spent at the medical organization for preventive medical examination	До 9 часов 10 минут / Up to 9 hours 10 minute	До 1 часа 20 минут / Up to 1 hour and 20 minutes
Сокращение времени ожидания в очереди перед кабинетом врача-специалиста / Reduction of the time of waiting in turn at consultation rooms (doctors-specialists, procedure unit)	20 минут / 20 minutes	0 минут / 0 minutes
Увеличение пропускной способности детей в смену (чел.) (план / факт) / Increase of admission capacity per shift (people) (plan/actual)	16 детей / 16 children	32 ребенка / 32 children

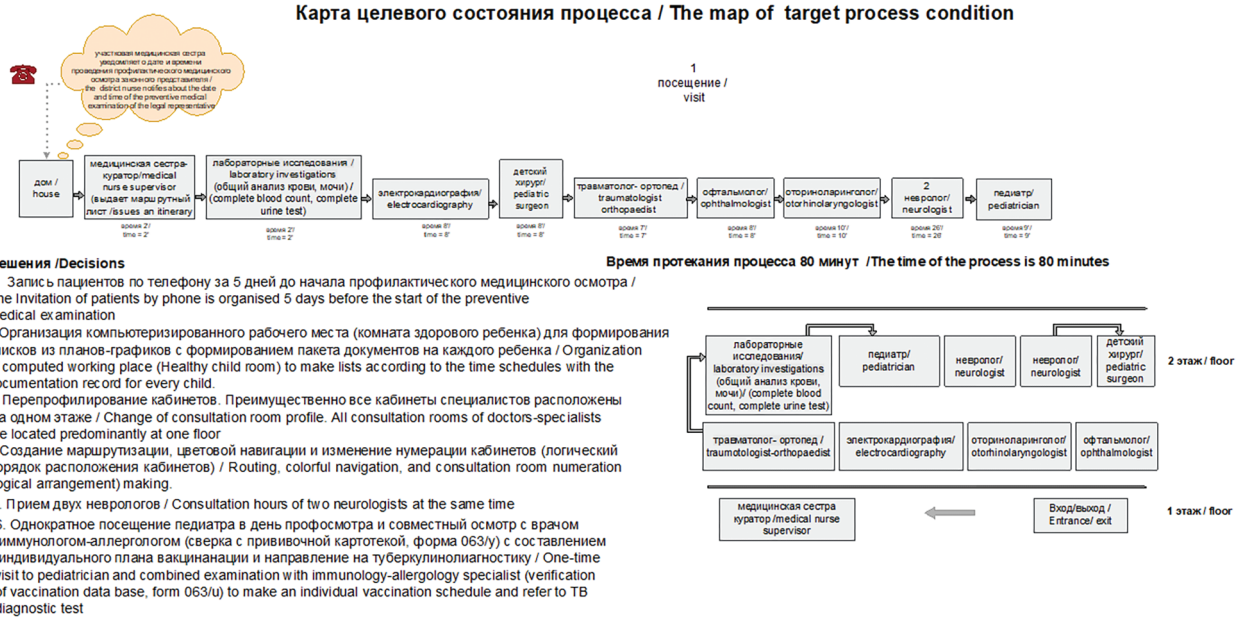

Fig. 3. Process map "Reducing the time for preventive medical examination of children aged 12 months (target condition)"

Рис. 3. Карта процесса «Сокращение времени прохождения профилактического медицинского осмотра детей в возрасте 12 месяцев (целевое состояние)»

- Streamlining of patient flows has been organized — the intersection of sick and healthy children, including those from different age categories, has been eliminated.
- A separate area has been set aside in the children's polyclinic, where specialist doctors' cabinets and a procedure room are concentrated side by side, and specific days and times for preventive medical examinations have been determined.
- The schedules of all specialist doctors involved in the preventive medical examination of children aged 12 months have a separate appointment time for this patient flow only (Thursday from 9:00 a.m. to 3:00 p.m.).
- For patients with an indication of the date, time of appointment by a specialist/examiner, the technology of preventive medical examination, developed in this polyclinic according to the "Carousel" principle, is implemented.

The "Carousel" technology consists in the fact that all types of examinations within the framework of medical check-up are concentrated in a separate block of the children's polyclinic. Lists of children needed the medical check-up are compiled for the Day of a Healthy Child. According to the list, the number of children is divided into groups of 8 people equal to the number of "Carousel" rooms, and each group is invited to a certain time. The administrator routes parents with children who have come for medical check-ups directly at the entrance to the children's polyclinic, which ensures that there is no overlap with other patients, and then parents with children are directed to the examination area. In the examination area, they are met by a nurse-curator and given a package of documents: a voluntary informed consent for a preventive medical examination, referrals for laboratory tests and an itinerary, which contains a list of tests and the time for each test. All patients start the examination in different rooms at the same time, and then, according to the itinerary, they change each other. After the first group has passed the medical checkup, the next group is invited in the same number of patients (Fig. 4).

- Standards of work of specialist doctors with uniform optimal time of tact have been developed and implemented.
- Clear and accessible navigation with prioritized flow for medical check-ups was developed.
- Information was improved and scripts were developed for district nurses and nurse supervisors to invite parents with a child to a medical checkup through modern telecommunication technologies (AI (artificial intelligence) to automate the initiation of sending targeted voice and text notifications to patients).
- An additional visit to a pediatrician to draw up a conclusion on the results of a medical checkup has been excluded from the process.
- A memo for parents has been developed for children undergoing medical checkups.
- All cabinets are standardized according to the 5C method.
- Monitoring has been implemented through systematic questionnaires to parents of patients and quarterly audits by the internal quality control service.

The implementation of the measures made it possible to achieve the following results:

- the number of patient visits to the outpatient clinic for medical checkup was reduced from 6 to 1;
- the patient's time in the medical organization for medical checkup decreased from 9 hours and 10 minutes to 1 hour and 20 minutes;
- queues at the cabinets disappeared;
- an increase in the number of admitted patients aged 12 months subject to medical checkups from 16 to 32 per shift;
- coverage of children of the appropriate age by medical checkups amounted to 100%;

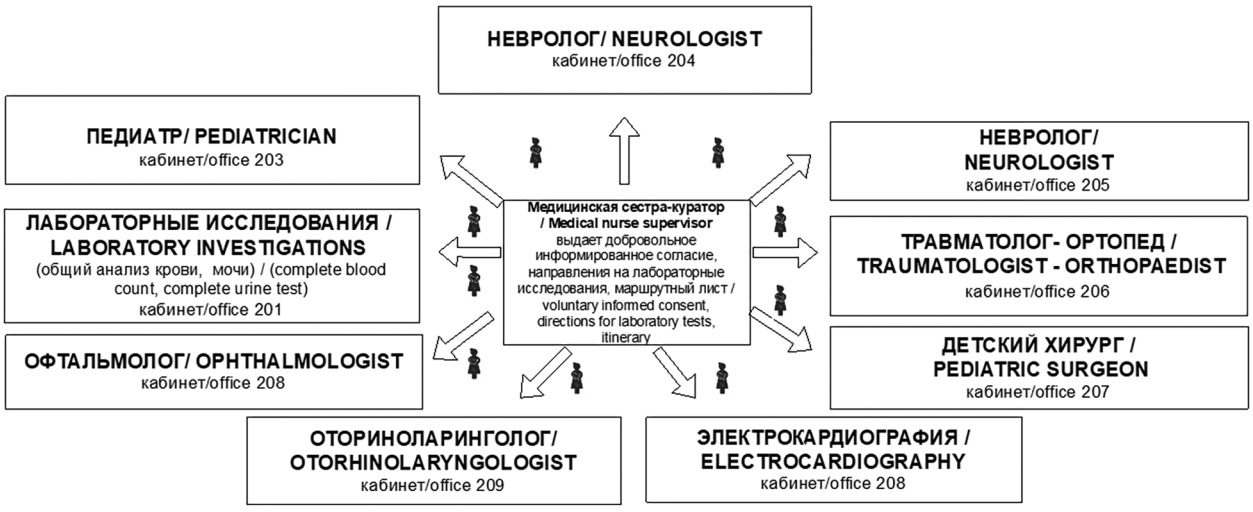

Fig. 4. Routing of children at the age of 12 months for preventive medical examination (according to the principle of "Merry-go-round")

Рис. 4. Маршрутизация детей в возрасте 12 месяцев при прохождении профилактического медицинского осмотра (по принципу «Каруселька»)

- parents' satisfaction with the organization of the process of medical checkups for their children, based on the results of a questionnaire survey, was 100%.

CONCLUSION

The application of lean production technologies improved the process of organizing medical checkups for children aged 12 months by increasing the availability and quality of medical care, which increased the value for the patient and parental satisfaction with the medical care provided. The successful experience of the children's polyclinic has been replicated in medical organizations providing primary health care to the pediatric population of St. Petersburg and the subjects of the Russian Federation.

ADDITIONAL INFORMATION

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

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

Funding source. This study was not supported by any external sources of funding.

Consent for publication. The authors received written consent from the respondents to publish the data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

Информированное согласие на публикацию. Авторы получили письменное согласие анкетируемых на публикацию данных.

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ISSN 2221-2582

UDC 616-083.98-053.2+616.33-083.2-036.11+616.329-002-085
DOI: 10.56871/CmN-W.2024.90.33.012

CLINICAL EFFICACY OF GASTRIC FEEDING WITH ANTIREFLUX MIXTURE IN PREMATURE INFANTS ON MECHANICAL VENTILATION

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For citation: Smirnov OG, Gorbachev VI. Clinical efficacy of gastric feeding with antireflux mixture in premature infants on mechanical ventilation**.** Children's Medicine of the North-West. 2024;12(3):110–115. DOI: https://doi.org/10.56871/CmN-W.2024.90.33.012

Received: 14.06.2024 **Revised: 29.07.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* Gastroesophageal reflux is a common pathological condition in critically ill premature infants. *The aim of the study* was to analyze the incidence of gastroesophageal reflux (GER) in premature infants and to evaluate the effectiveness of gastric feeding with antireflux mixture in children on artificial ventilation in the presence of GER. *Materials and methods.* A retrospective study was conducted on the basis of the Irkutsk Municipal Pediatric Clinical Hospital (Irkutsk) in the period from 2018 to 2020, which included the medical histories of 73 premature infants. In the course of the study, the frequency of GER, the frequency of use of antireflux drugs, changes in body weight during the period of stay in intensive care, the duration of ventilation, the duration of stay in intensive care and changes in laboratory parameters at the time of admission and 10 days after the start of intensive care were evaluated. *Results and discussion.* A retrospective analysis showed that 69.8% of the total number of children in the medical history had any records of manifestations of gastroesophageal reflux. When clinical manifestations of GER occurred, the frequency of transfer to an antireflux mixture was in 100% of cases, of which 52.4% received medication (motilium, omeprazole) during hospitalization in intensive care, and 19.6% continued to receive it after transfer to the department. Among those who received antireflux mixtures, GER was diagnosed in only 47% of patients. Among all newborns who received the drugs, 62.7% of patients received motilium and 35.2% omeprazole. With the ineffectiveness of conservative antireflux therapy, surgical fundoplication was performed in 17.6% of patients. *Conclusion.* Conservative antireflux therapy for gastric feeding in premature infants with low and very low body weight, with pneumonia, on artificial lung ventilation does not provide sufficient effectiveness of child nutrition.

Keywords: *intensive care in neonatology, enteral feeding, antireflux therapy*

КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ГАСТРАЛЬНОГО КОРМЛЕНИЯ АНТИРЕФЛЮКСНОЙ СМЕСЬЮ У НЕДОНОШЕННЫХ ДЕТЕЙ НА ИСКУССТВЕННОЙ ВЕНТИЛЯЦИИ ЛЕГКИХ

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Для цитирования: Смирнов О.Г., Горбачев В.И. Клиническая эффективность гастрального кормления антирефлюксной смесью у недоношенных детей на искусственной вентиляции легких // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 110–115. DOI: https://doi.org/10.56871/CmN-W.2024.90.33.012

Поступила: 14.06.2024 **Одобрена: 29.07.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение.* Гастроэзофагеальный рефлюкс — часто возникающее патологическое состояние у недоношенных новорожденных детей в критическом состоянии. *Цель исследования* — проанализировать

частоту развития гастроэзофагеального рефлюкса (ГЭР) у недоношенных детей и оценить эффективность гастрального кормления антирефлюксной смесью у детей на искусственной вентиляции легких при наличии ГЭР. *Материалы и методы.* На базе Областного государственного автономного учреждения здравоохранения «Городская Ивано-Матрёнинская детская клиническая больница» (г. Иркутск) в период с 2018 по 2020 гг. было проведено ретроспективное исследование, в которое были включены истории болезни 73 недоношенных детей. В процессе исследования оценили частоту ГЭР, частоту использования антирефлюксных препаратов, изменение массы тела за период нахождения в реанимации, длительность ИВЛ, продолжительность пребывания в реанимации и изменения лабораторных показателей на момент поступления и через 10 дней после начала интенсивной терапии. *Результаты и обсуждение.* Проведенный ретроспективный анализ показал, что у 69,8% детей в истории болезни были какие-либо записи о проявлениях гастроэзофагеального рефлюкса. Все пациенты при возникновении клинических проявлений ГЭР получали антирефлюксную смесь, из них у 52,4% проводили медикаментозное лечение (мотилиум, омепразол) во время госпитализации в реанимации, а 19,6% продолжали получать их и после перевода в отделение патологии новорожденных. Среди тех, кто получал антирефлюксные смеси, ГЭР был диагностирован только у 47% пациентов. Из всех новорожденных, получавших препараты, 62,7% пациентов получали мотилиум и 35,2% омепразол. При неэффективности консервативной антирефлюксной терапии 17,6% пациентов была выполнена оперативная фундопликация. *Заключение.* Проведение консервативной антирефлюксной терапии при гастральном кормлении у недоношенных детей с низкой и очень низкой массой тела, с пневмонией, на искусственной вентиляции легких не обеспечивает достаточной эффективности питания ребенка.

Ключевые слова: *интенсивная терапия в неонатологии, энтеральное кормление, антирефлюксная терапия*

INTRODUCTION

Gastroesophageal reflux (GER) is a pathologic condition that often occurs in premature infants in critical condition. A number of factors contribute to this condition: a relatively large volume of liquid food intake, functional "immaturity" of the lower esophageal sphincter, and the position of the child's body when feeding — the child lying on the back [1]. Determining the exact prevalence of GER versus gastroesophageal reflux disease (GERD) is a difficult task because of the unclear distinction between physiologic and pathologic reflux.

Conservative treatment should be considered as first-line therapy in infants without clinical complications [2]. Based on the available data, body positioning can be considered a well-established and safe method for the treatment of preterm infants with symptoms of uncomplicated GER. A reduction in GER manifestations is observed in the left lateral position with the head elevated, whereas the supine and right side positions provoke reflux [3]. In addition, certain benefits can be achieved by modifying the diet and/or duration of feeding, such as reducing the feeding rate and using hydrolyzed formula [4]. The use of transpyloric feeding is an effective feeding method, allows faster stabilization of nutritional balance and substantial weight gain [4]. Gum used to thicken the food clump has been found to impede the absorption of a number of nutrients [5, 6]. There have also been concerns about a possible association between formula thickener and the development of necrotizing enterocolitis [7]. Antireflux medications, including histamine-2 receptor antagonists and proton pump inhibitors, are not licensed for use in newborns in the Russian Federation (RF) and many other countries, although *off label* use (use of medications for indications not mentioned in the instructions for use) is often reported [8]. Antacids and other acid-suppressing drugs can reduce gastric acidity but do not affect the signs/symptoms of GER, and their use is associated with an increased risk of adverse outcomes, including necrotizing enterocolitis (NEC) and infections [9]. A number of researchers recommend the use of antireflux medications with caution (if it is possible) in preterm infants because of the lack of evidence of efficacy and possible harm [10].

AIM

To analyze the incidence of gastroesophageal reflux (GER) in preterm infants and to evaluate the efficacy of gastric feeding with antireflux formula in infants on artificial lung ventilation in the presence of GER.

MATERIALS AND METHODS

A retrospective study was conducted. It included 73 case histories of premature infants treated

 ISSN 2221-2582

in the neonatal intensive care unit of the Ivano-Matryoninsky Children's Clinical Hospital (Irkutsk city) in the period from 2018 to 2020. Patients included in the study were born prematurely at 28–35 weeks of gestation with low and very low weight, required ventilatory support and had a confirmed diagnosis of pneumonia.

The patients in the generated sample were divided into two groups. The first group consisted of 51 patients with confirmed gastroesophageal reflux. The second group consisted of 22 patients without GER. Respiratory therapy in the intensive care unit was performed in the PCV (pressure-controlled ventilation) mode using a MAQUET Servo-i ventilator (Germany).

In the course of the study, we evaluated the frequency of GER, ALV and changes in laboratory parameters at the time of admission and 10 days after the start of intensive care.

Statistical processing of the obtained data was performed using STATISTICA 10.0 program. The results are presented as median and quartiles (25–75%). Statistical analysis of significance of differences between quantitative signs for two independent groups was performed using the Mann–Whitney criterion. The Kraskell-Wallis test was used to assess the statistical significance of differences between several signs in dynamics. The p value <0.05 was taken as the level of statistical significance.

RESULTS

Retrospective analysis of medical records showed that 69.8% (n=51) of children had any records of gastroesophageal reflux manifestations in their medical history. Gestational age in the group of children with GER was 31 (28–35) weeks and in the group without GER it was 32 (28–36) weeks. Age at the time of admission was 19 (10–77) days in the group with GER and 17 (9–65) days in the group without GER. At the onset of clinical manifestations of GER, 100% of patients received antireflux medication, of which 27 patients (52.4%) received medication (motilium, omeprazole) during ICU hospitalization, and 19.6% (n=10) continued to receive them even after transfer from the ICU. Among those who received therapeutic (antireflux) formula, GER was diagnosed in 47% (n=24) of patients. Among all neonates receiving medication, 62.7% (n=32) of patients received motilium and 35.2% (n=18) received omeprazole. If conservative antireflux therapy was ineffective, 9 (17.6%) patients underwent surgical fundoplication (Fig. 1).

In analyzing of the weight dynamics on the 10th day from the beginning of conservative antireflux therapy it was found that children diagnosed with GER had a lower weight gain of 11 (9–14) g compared to patients without reflux 17 (14.5–18) g (p_U <0.01). When analyzing the weight of patients on the 10th day of conservative antireflux therapy

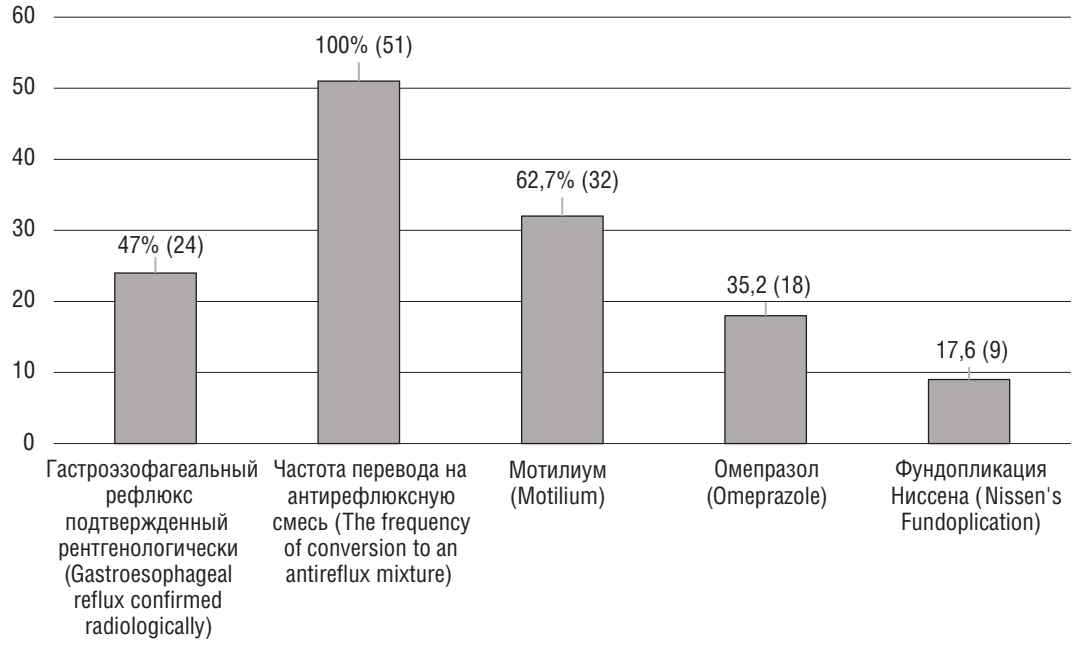

Fig. 1. Retrospective analysis

Рис. 1. Ретроспективный анализ

we managed to reveal statistically significant differences. Thus, weight in children with GER was 1979 (1759–2100) g, in patients without gastroesophageal reflux it was 2247 (2090–2337.5) g (p_U <0.01) (Fig. 2). Intensive care stay time in children diagnosed with GER was significantly higher than in children without GER, 12 (9.5–14.5) days versus 17 (15–20) days (p_U <0.01).

The rates of length of hospital stay in children with GER were 49 (34–74) days versus 37 (34–46) days in children without GER (p_U <0.01). The level of total protein in patients with GER on the first day was 39.2 (35.3–53.3) g/L. Control of this parameter on the 10th day revealed a decrease in the concentration of total protein to 34.1 (30.9–48.2) g/L. Total protein in the group of children without GER on the first day was 40.2 (38.1–51.3) g/L, on the 10th day in the group of children without GER the level of total protein was 46.9 (42.2–50.8) g/L (Fig. 3).

Creatinine in children with GER on the first day was at the level of 54.4 (28.2–56.5) μmol/L. In the group of children without gastroesophageal reflux it was 49.1 (33.3–58.7) μmol/L. On the 10th day of the study there were also no significant changes in the studied groups. Thus, the creatinine level in the group with GER — was 50.5 (30.3–53.9) μmol/L, in the group of children without GER it was 54.3 (30.2–52.6) μmol/L. Comparable results were obtained when analyzing urea levels. In the group of children with reflux in the first day of stay in the Department of Anesthesiology, Reanimation and Intensive Care urea was 3.0 (2.2–3.5) mmol/L, on the 10th day of observation it was 4.0 (3.0–4.8) mmol/L. In the group of children without GER it was 3.2 (2.5–3.9) mmol/L, on the 10th day of observation it was 4.1 (3.2–5.4) mmol/L. Glucose level in the group of children with GER on the first day was 4.2 (3.6–7.1) mmol/L, in the group of children without GER it was 4.9 (3.8–5.1) mmol/L. Thus, in the group of children with GER the glucose level was 5.9 (3.3–7.8) mmol/L, in the group without GER it was 5.3 (4.5–6.9) mmol/L. The level of K^+ in the group of children with gastroesophageal reflux on admission was 4.1 (3.5–4.5) mmol/L, in the group of children without GER it was 3.9 (3.4–4.2) mmol/L. The study of K^+ level in dynamics did not reveal statistically significant changes: on the 10th day of the study in the group of children with gastroesophageal reflux the level of K^+ was 3.8 (3.5–4.2) mmol/L, in the group of children without GER it was 4.1 (4.0–5.3) mmol/L. Na^+ concentration in the group of children with gastroesophageal reflux on admission was 137.5 (136.0–142.6) mmol/L, in the group of children without GER it was 139.3 (137.0–141.6) mmol/L. When studying the level of Na^+ concentration in dynamics, no statistically significant differences were found: on the 10th day of the study in the group of children with GER the Na^+ level was 138.10 (136.4–141.6) mmol/L, in the group without GER it was 138.1 (136.6–140.9) mmol/L. Plasma Ca^{2+} concentration in the group of children with GER at admission was 1.15 (1.1–1.5) mmol/L, in the group without GER it was 1.3 (1.1–1.4) mmol/L. On the 10th day of the study, in the group of children with gastroesophageal reflux the Ca^{2+} level was 1.1 (1.1–1.3) mmol/L, in the group of children without GER it was 1.3 (1.0–1.4) mmol/L.

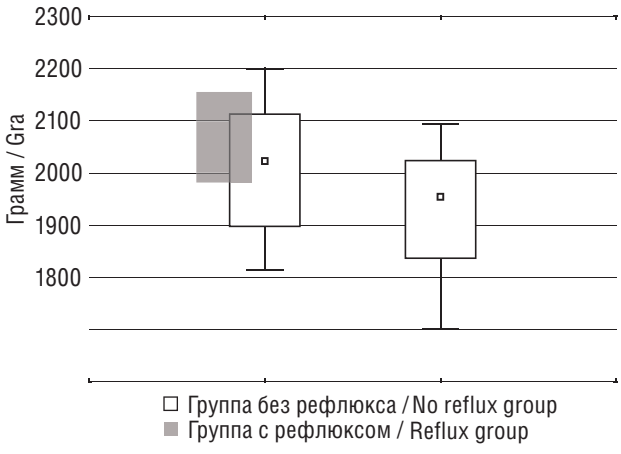

Fig. 2. Weight on the 10th day of antireflux therapy

Рис. 2. Масса тела на 10-й день проводимой антирефлюксной терапии

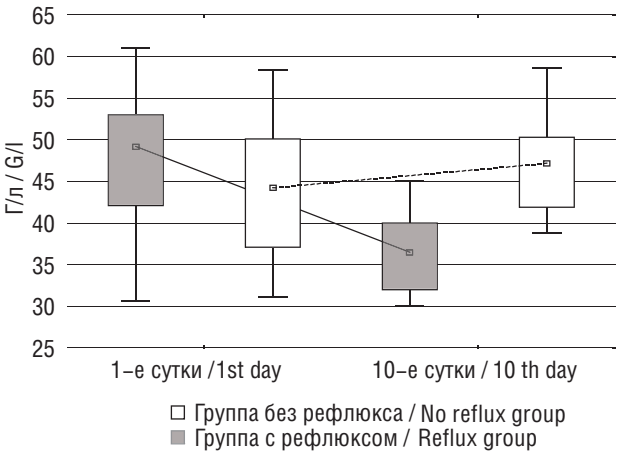

Fig. 3. Total protein level

Рис. 3. Изменения уровня общего белка

DISCUSSION

It was found that children with reflux had lower birth weight and gestational age during comparing patients with gastroesophageal reflux with patients without GER. This may be due to the fact that transient relaxation of the lower esophageal sphincter is more common in preterm infants. An interesting finding was that the incidence of using drugs for conservative therapy of GER was higher than the incidence of documented GER. This indicates that drugs for conservative therapy of GER are prescribed without a confirmed diagnosis. In our analysis, we found that manifestations of GER occurred in 69.8% of patients, while the rate of switching to antireflux formula was 100% of cases. However, among infants receiving antireflux treatment, gastroesophageal reflux was confirmed radiologically in only 39.6%. In 36.9% of cases, infants received medication during hospitalization in the intensive care unit, and 18.2% of patients continued to receive medication after they were transferred. We noted a high level of use of drug therapy in preterm infants: in 57% of cases motilium was prescribed, in 45.4% of cases children received proton pump inhibitors (omeprazole). When analyzing weight dynamics, it was found that the average daily weight gain in children with reflux was 32.2% less than in children without GER. The concentration of total protein in children with GER was also 14.2% lower than in children without GER. Due to ineffectiveness of conservative therapy, 17.6% of patients underwent fundoplication.

CONCLUSION

Conservative antireflux therapy with gastral feeding in premature infants with low and very low weight, with pneumonia, on artificial lung ventilation does not provide sufficient effectiveness of feeding the child.

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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ISSN 2221-2582

UDC 616.4-001.3
DOI: 10.56871/CmN-W.2024.33.14.013

STUDY OF ORAL FLUID TRACTABILITY AS A TENTATIVE TEST FOR DETERMINING AN UNFAVORABLE SITUATION IN THE ORAL CAVITY IN YOUNG PEOPLE

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For citation: Belogortseva AN, Iordanishvili AK. Study of oral fluid tractability as a tentative test for determining an unfavorable situation in the oral cavity in young people. Children's Medicine of the North-West. 2024;12(3):116–120. DOI: https://doi.org/10.56871/CmN-W.2024.33.14.013

Received: 11.06.2024 **Revised: 24.07.2024** **Accepted: 10.09.2024**

Abstract. At present there is little information about the possibility of using the test spinnbarkeit, which allows to establish the extensibility of saliva, although the possibility of its use with the exclusion of the laboratory stage has been proved, which allowed in the clinical practice of dentists to replace complex and time-consuming tests such as the secretion rate and viscosity of oral fluid (mixed saliva). The paper evaluated the possibility of using the oral fluid viscosity test in young people, taking into account their incidence of underlying dental pathology, as well as concomitant diabetes mellitus. Sixty-five people of young age were under observation and were divided into two groups depending on the concomitant pathology. Group 1 included 34 people who were somatically healthy. Group 2 included 31 people who suffered from diabetes mellitus. It was found that the patients of group 1 of the study according to the index of the intensity of dental caries (CPU) can be attributed to the group of people with subcompensated, and patients of group 2 — to decompensated activity of dental caries. This is due to satisfactory oral hygiene in group 1 patients and unsatisfactory oral hygiene in group 2 patients, as well as due to the established increased saliva tractability in group 2 patients. It is shown that the technique of determination of mixed saliva tractability can be used as an additional method in the study of dental status, as well as risk factors for demineralization of hard tissues of teeth and inflammatory periodontal pathology, provided that it is easy to perform and sufficiently informative.

Keywords*: young people, oral fluid, mixed saliva, dental caries, resistance of dental hard tissues, intensity of dental caries, oral hygiene, periodontal pathology, saliva viscosity, microcrystallization of saliva*

ИССЛЕДОВАНИЕ ТЯГУЧЕСТИ РОТОВОЙ ЖИДКОСТИ КАК ОРИЕНТИРОВОЧНЫЙ ТЕСТ ОПРЕДЕЛЕНИЯ НЕБЛАГОПРИЯТНОЙ СИТУАЦИИ В ПОЛОСТИ РТА У МОЛОДЫХ ЛЮДЕЙ

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Для цитирования: Белогорцева А.Н., Иорданишвили А.К. Исследование тягучести ротовой жидкости как ориентировочный тест определения неблагоприятной ситуации в полости рта у молодых людей // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 116–120. DOI: https://doi.org/10.56871/CmN-W.2024.33.14.013

Поступила: 11.06.2024 **Одобрена: 24.07.2024** **Принята к печати: 10.09.2024**

Резюме. В настоящее время мало сведений о возможности использования теста spinnbarkeit, позволяющего установить растяжимость слюны, хотя доказана возможность его использования при исключении

лабораторного этапа, что позволило в клинической практике врачей-стоматологов заменить сложные и продолжительные по времени тесты, такие как скорость секреции и вязкость ротовой жидкости (смешанной слюны). В работе оценена возможность использования теста на тягучесть ротовой жидкости у людей молодого возраста с учетом их заболеваемости основной стоматологической патологии, а также сопутствующего сахарного диабета. Под наблюдением находилось 65 людей молодого возраста, которые в зависимости от сопутствующей патологии были разделены на две группы. В 1-ю группу вошли 34 человека, которые соматически были здоровы. Во 2-ю группу вошел 31 человек, страдающих сахарным диабетом. Установлено, что пациентов 1-й группы исследования по показателю индекса индекс интенсивности течения кариеса зубов (КПУ) можно отнести к группе людей с субкомпенсированнной, а пациентов 2-й группы — к декомпенсированной активностью кариеса зубов. Это связано с удовлетворительной гигиеной рта у пациентов 1-й группы и неудовлетворительной гигиеной рта у пациентов 2-й группы, а также в связи с установленной повышенной тягучестью слюны у пациентов 2-й группы. Показано, что методика определения тягучести смешанной слюны может использоваться в качестве дополнительного метода при исследовании стоматологического статуса, а также факторов риска возникновения деминерализации твердых тканей зубов и воспалительной патологии пародонта при условии простоты ее выполнения и достаточной информативности.

Ключевые слова: *люди молодого возраста, ротовая жидкость, смешанная слюна, кариес зубов, резистентность твердых тканей зубов, интенсивность кариеса зубов, гигиена полости рта, патология пародонта, тягучесть слюны, микрокристаллизация слюны*

INTRODUCTION

Currently, there is an opinion that dental caries is the initial symptom of a nonspecific infectious disease of the masticatory apparatus, provoked and maintained by a number of factors. The main ones being reduced resistance (permeability) of dental hard tissues, as well as poor oral hygiene and frequent consumption of carbohydrate-containing foods [1, 2].

In addition to determining the quality of dental care using oral hygiene indices, laboratory methods to diagnose the cariesogenic situation or so-called saliva tests are considered important. In the literature, salivary microcrystallization in patients of different age groups is the most frequently reported [3, 4]. At the same time, there is little information about the possibility of using the saliva tractability test to establish its extensibility, although the possibility of its use in the clinical practice of dentists to replace complex and time-consuming tests such as the secretion rate and viscosity of oral fluid (mixed saliva) has been proven [5, 6].

AIM

The aim of the study is to evaluate the feasibility of using the oral fluid tractability test in young adults, taking into account their incidence of major dental pathology as well as comorbidities.

MATERIALS AND METHODS

There were 65 (38 (58.47%) males and 27 (41.53%) females) young people (18 to 25 years old) under observation, who were divided into two groups depending on the concomitant pathology. Group 1 included 34 (26 (76.47%) males and 8 (23.53%) females) people who were somatically healthy. Group 2 included 31 (12 (38.71%) males and 19 (61.29%) females) individuals who had type 1 or type 2 diabetes mellitus. All patients in group 2 were under dynamic observation by a district endocrinologist and were continuously receiving insulin therapy, but they were not under dynamic observation by a dentist.

During the dental examination, the following parameters were investigated in patients:

1) CFE index (sum of carious, filled and extracted teeth) according to the generally accepted method [7];
2) simplified Green-Vermillion index (OHI-S) to assess the state of oral hygiene [7];
3) the method of determining the pulling power of oral fluid according to the method of P.A. Leus and L.V. Belyasova [8].

Dental examinations were performed once and the character of dental health of the examined patients in both study groups was assessed based on the obtained indicators.

The digital material obtained in the clinical study was processed on a personal computer using a specialized package for statistical analysis STATISTICA 6.0. Differences between the compared groups were considered reliable at $p \leq 0.05$. Cases when the probability values of "p" were in the range from 0.05 to 0.10 were considered as "presence of a tendency".

RESULTS AND DISCUSSION

During the clinical study, it was found that the young patients of study group 1 had good

 ISSN 2221-2582

oral hygiene (simplified Green–Vermillion index (OHI-S) was 0.61±0.19) and the CFE index was 5.62±1.56. In patients of group 2 of the study, who had diabetes mellitus, oral hygiene was unsatisfactory (simplified Green–Vermillion index (OHI-S) was 2.36±0.37, p <0.05), and the CFE index was 10.46±2.44, p <0.05 (Fig. 1). Figure 2 shows the distribution of the CFE index according to the number of carious, filled and extracted teeth. It can be said that patients of the 1st group of the study according to the index of the CFE index can be attributed to the group of people with subcompensated, and patients of the 2nd group — with decompensated activity of dental caries (Fig. 2). The observed differences in caries intensity between the two groups of subjects were significant (p <0.01). Despite the fact that sanitation measures were necessary for all people from both study groups, the patients of group 2 obligatorily required professional oral hygiene, which provides not only real therapeutic and preventive measures, but also training of patients in individual dental hygiene.

The study of oral fluid tractability (mixed saliva) showed that 29% of group 1 patients had "short salivary tractability", i.e. salivary filament breakage occurred in the oral cavity, immediately below the cutting edges of the maxillary central incisors . Only 5% of patients in this group had "medium salivary tractability", in which salivary filament breakage occurred at the level from the upper lip to the tip of the nose [8]. Group 2 patients were significantly characterized by "long salivary tractability", which was noted in 27% of patients, and 7% of patients from this group had "medium salivary extensibility" (Fig. 3).

Thus, the young patients of the study group 2 with diabetes mellitus had significantly higher salivary tractability than the patients of group 1 (p <0.01).

The clinical method of assessing salivary tractability is imperfect, as its results can be affected by many factors that are difficult to take into account or exclude at an outpatient dental appointment. However, it should be noted the high diagnostic value of this technique, which indirectly allows us to judge a number of physical and chemical properties of oral fluid, namely the viscosity of saliva, as well as the rate of its secretion, on which largely depends on the biochemical composition of oral fluid and its viscosity [9]. Our use of the interpretation of the previously proposed degree of saliva tractability into "short, medium and long salivary extensibility" [8] coincided with the intensity of the course of dental caries and the nature of oral hygiene. That is, with the increase of saliva tractability with a high

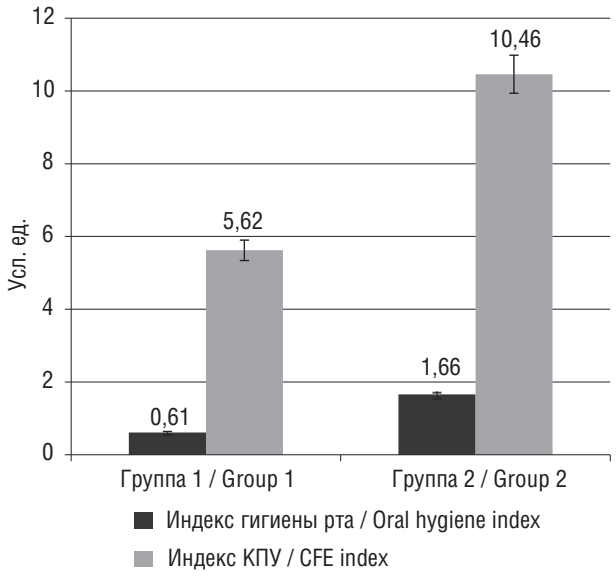

Fig. 1. Indicators of the Green–Vermillion (OHI-S) and the CFE index in patients of the study groups (arbitrary units)

Рис. 1. Показатели индекса гигиены рта Грина–Вермиллиона (OHI-S) и индекса КПУ у пациентов обследуемых групп (усл. ед.)

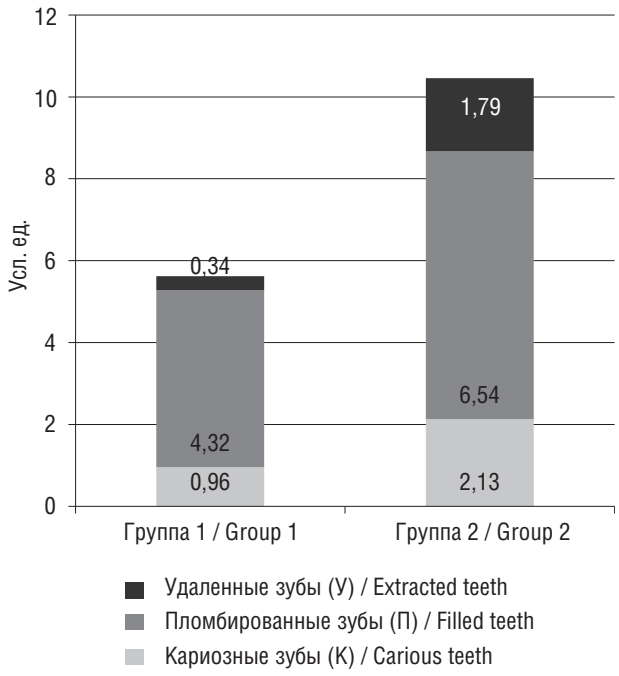

Fig. 2. Characteristics of the intensity of the carious process according to the CFE index in patients of both study groups (arbitrary units)

Рис. 2. Характеристика интенсивности течения кариозного процесса по показателю индекса КПУ у пациентов обеих групп исследования (усл. ед.)

degree of objectivity we can assume the increase of cariesogenic situation in the oral cavity, as well as the threat of the development of inflammatory periodontal lesions and the formation of soft and mineralized deposits on the crown parts of teeth, which is confirmed by the deterioration of oral hygiene in patients of the 2nd group of the study. It should be assumed that young patients suffering from diabetes mellitus, in addition to medical follow-up by an endocrinologist, should be under the observation by a dentist, which has a pronounced effect of improving the quality of dental health in such patients [10].

CONCLUSION

The performed clinical study on the evaluation of the use of the oral fluid pull test in young people with regard to their dental pathology, as well as concomitant diabetes mellitus, has shown that the tested method can be used as an additional method in the study of dental status and risk factors for demineralization of hard tissues of teeth and inflammatory periodontal pathology. The method of saliva tractability test is simple to perform and quite informative. With an increase in saliva extensibility with a high degree of objectivity should be assumed an increase in cariesogenic situation in the oral cavity, as well as the threat of inflammatory periodontal lesions.

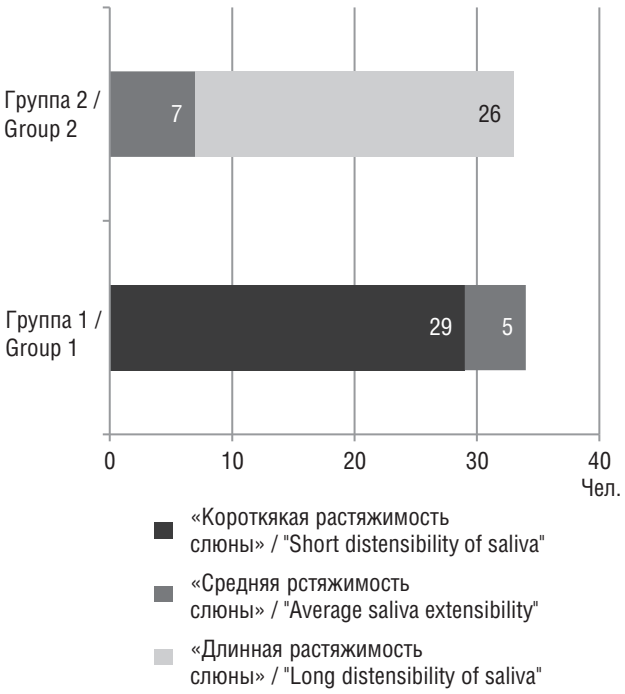

Fig. 3. Characteristics of the viscosity of oral fluid (mixed saliva) in patients of both study groups (persons)

Рис. 3. Характеристика тягучести ротовой жидкости (смешанной слюны) у пациентов обеих групп исследования (чел.)

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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UDC 616-002.77-085-07-08+614.2+369.223.223
DOI: 10.56871/CmN-W.2024.77.77.014

ISSUES OF OUTPATIENT RHEUMATOLOGY CARE FOR CHILDREN IN ST. PETERSBURG (USING THE EXAMPLE OF ST. MARY MAGDALENE CHILDREN'S CITY HOSPITAL № 2)

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For citation: Santimov AV, Tamm OA. Issues of outpatient rheumatology care for children in Saint Petersburg (using the example of St. Mary Magdalene Children's City Hospital № 2). Children's Medicine of the North-West. 2024;12(3):121–129. DOI: https://doi.org/ 10.56871/CmN-W.2024.77.77.014

Received: 31.05.2024 **Revised: 02.08.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* The effectiveness of providing specialized rheumatological care to the pediatric population directly depends on the completeness and quality of data on the prevalence of rheumatic diseases in children, the analysis of which takes into account not only the number of patients with rheumatic diseases, but also the peculiarities of their course and routing ("portrait" and "pathway" of the patient). *Purposes and tasks.* Describe the "pathway" and "portrait" of all patients who have applied for an outpatient appointment with a rheumatologist for 5 months. *Materials and methods.* During outpatient appointments, the rheumatologist recorded the age and gender, the patient's complaints, the diagnosis of the referral, the previously prescribed therapy, for primary patients it was additionally clarified which specialist referred them for consultation, and whether they had a full primary diagnosis. Based on the results of the admission, the established diagnosis and prescribed therapy were recorded, the frequency of fundamental differences in diagnoses and cases of inadequate therapy, the frequency of referrals of patients to emergency and planned hospitalization in the rheumatology department were recorded. *Results.* The "pathway" and "portrait" of all patients who applied for an outpatient appointment with a rheumatologist for 5 months are presented. Of the 335 receptions conducted, there were 204 (60.9%) initial applications, 131 (39.1%) repeated ones. A fundamental discrepancy between the diagnosis of the referral and the diagnosis established during the consultation was recorded in 53 cases (15.82%). In 15 cases (4.48%), there was a clear inadequacy of the therapy carried out before the consultation with a rheumatologist. Among the 204 patients examined by a rheumatologist initially, only 168 (82.35%) had the minimum necessary laboratory tests, joint radiography in 119 (58.33%), ultrasound examination of joints in 84 (41.18%). *Conclusions.* It is necessary to increase the provision of outpatient rheumatologists and increase the level of training in the diagnosis and treatment of rheumatic diseases among specialists who perform the functions of rheumatologists in their absence.

Keywords*: rheumatic diseases, children, outpatient admission*

ВОПРОСЫ ОКАЗАНИЯ АМБУЛАТОРНОЙ РЕВМАТОЛОГИЧЕСКОЙ ПОМОЩИ ДЕТЯМ В САНКТ-ПЕТЕРБУРГЕ (НА ПРИМЕРЕ ДЕТСКОЙ ГОРОДСКОЙ БОЛЬНИЦЫ № 2 СВЯТОЙ МАРИИ МАГДАЛИНЫ)

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Для цитирования: Сантимов А.В., Тамм О.А. Вопросы оказания амбулаторной ревматологической помощи детям в Санкт-Петербурге (на примере Детской городской больницы № 2 Святой Марии Магдалины) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 121–129. DOI: https://doi.org/10.56871/CmN-W.2024.77.77.014

Поступила: 31.05.2024 **Одобрена: 02.08.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение.* Эффективность оказания специализированной ревматологической помощи детскому населению напрямую зависит от полноты и качества данных о распространенности ревматических заболеваний у детей, при анализе которой учитываются не только численность пациентов с ревматическими заболеваниями, но и особенности их течения и маршрутизации («портрет» и «путь» пациента). *Цели и задачи.* Описать «путь» и «портрет» всех пациентов, обратившихся на амбулаторный прием врача-ревматолога в течение 5 месяцев. *Материалы и методы.* В ходе амбулаторных приемов врачом-ревматологом фиксировался возраст и пол, жалобы пациента, диагноз направления, назначенная ранее терапия, для первичных пациентов дополнительно уточнялось, какой специалист направил их на консультацию, и была ли им проведена первичная диагностика в полном объеме. По результатам приема записывали установленный диагноз и назначенную терапию, фиксировали частоту принципиальных расхождений диагнозов и случаев неадекватной терапии, частоту направлений пациентов на экстренную и плановую госпитализацию в ревматологическое отделение. *Результаты*. Представлен «путь» и «портрет» всех пациентов, обратившихся на амбулаторный прием врача-ревматолога в течение 5 месяцев. Из 335 проведенных приемов было 204 (60,9%) первичных обращения и 131 (39,1%) повторное. Принципиальное расхождение диагноза направления и диагноза, установленного в ходе консультации, было зафиксировано в 53 случаях (15,82%). В 15 случаях (4,48%) была отмечена явная неадекватность проводимой до консультации ревматолога терапии. Среди 204 пациентов, осмотренных ревматологом первично, только у 168 (82,35%) были выполнены минимально необходимые лабораторные исследования, рентгенография суставов — у 119 (58,33%), ультразвуковое исследование суставов — у 84 (41,18%). *Выводы.* Необходимо повышение обеспеченности амбулаторного звена врачами-ревматологами и повышение уровня подготовки в вопросах диагностики и лечения ревматических заболеваний у специалистов, выполняющих функции врачей-ревматологов в их отсутствие.

Ключевые слова*: ревматические заболевания, дети, амбулаторный прием*

INTRODUCTION

At the beginning of the XXI century there was a clear tendency to increase the number of diagnosed rheumatic diseases in children in the Russian Federation, like all over the world [1, 2]. The effectiveness of providing specialized, high-tech, rheumatological care to children directly depends on the availability and quality of data on the prevalence of rheumatic diseases in children. Analysis of the obtained information should take into account the number of patients with rheumatic diseases, as well as peculiarities of the course of these diseases and patient routing ("portrait" and "path" of a patient, respectively) [2, 3]. The main problems faced by patients at the beginning of this "pathway" are an insufficient supply of rheumatologists in outpatient care and insufficient training in the diagnosis and treatment of rheumatic diseases among specialists who are forced to perform their functions (paediatricians, general practitioners, orthopaedic traumatologists, paediatric cardiologists and other outpatient specialists) [2, 4]. At the same time, our own experience in providing outpatient rheumatological care in the Russian Federation is published very rarely, both as an example of adult patients [5, 6] and children [7, 8]. Children's City Hospital (CCH) N 2 of St. Mary Magdalene is the only city hospital in St. Petersburg that has a rheumatology department in its structure, and its Consultative and Diagnostic Centre (CDC) has the largest number of paediatric rheumatologists (both staff units and individuals) [9, 10]. The analysis of the sample of patients referred to the outpatient rheumatologist of the CDC of Children's Hospital N 2 largely reflects the general situation with outpatient rheumatological care for children in St. Petersburg.

AIM

The aim of the research is to describe a "path" and 'portrait' of all patients who applied to an outpatient appointment to one of the rheumatologists of the CDC of CCH N 2 within 5 months.

MATERIALS AND METHODS

From 4 October 2023 to 6 March 2024, a rheumatologist working part-time at CDC CCH N 2 conducted 335 outpatient appointments for children aged 10 months to 18 years (median 10.1 years). During the appointments, the age and gender of

a patient were recorded, it was specified whether it was a primary or a repeat appointment (patients who came to see this rheumatologist for the first time but had previously consulted other rheumatologists were recorded separately). Patients who were referred for consultation were specified for primary patients (outpatient clinic doctors — paediatrician, orthopaedic traumatologist, paediatric surgeon, paediatric cardiologist, paediatrician of the reception department of the Children's Hospital N 2, specialist doctors of the CDC of the Children's Hospital N 2). Patient's complaints, referral diagnosis, previously prescribed therapy were recorded. In case of primary patients, it was additionally specified whether primary diagnostics (laboratory, ultrasound and radiological) had been carried out in full. According to the results of an appointment, there were recorded diagnoses and prescribed therapy, the frequency of fundamental discrepancies between the diagnoses established before and after the appointment, as well as the frequency of cases of inadequate previously prescribed therapy, and referrals for emergency and planned hospitalization in rheumatology departments. The information obtained was entered into an electronic database using Microsoft Office Excel 2016 software. Qualitative features were analyzed in the study and presented in the form of absolute numbers (n) and extensive indicators (%).

RESULTS

The distribution of patients classified by age and sex is presented in Table 1.

204 (60.9%) primary referrals and 131 (39.1%) repeat referrals were recorded out of 335 appointments in total. Among the primary patients, 54 (16.12% of the total number of patients) had ever been previously seen by other rheumatologists both at CCH N 2 and other medical institutions, 150 patients (44.78% of all admissions) were seen by a rheumatologist for the first time. Among them 50 patients (33.33%) were referred by paediatricians of polyclinics, 33 patients (22%) were referred by paediatricians of the reception department of CCH N 2, 32 patients (21.33%) were referred by orthopaedic traumatologists, 9 patients (6%) were referred for planned rheumatologist consultation after discharge from paediatric departments of CCH N 2, 6 patients (4%) were referred by ORLs of outpatient clinics, 4 patients (2.67%) were referred by surgeons of outpatient clinics, 3 patients (2%) were referred by cardiologists, gastroenterologists, allergologists, 2 patients (1.33%) were referred by infectious disease specialists and ophthalmologists, and 1 patient (0.67%) was referred by a nephrologist, dermatologist and neurologist.

Among 335 patients referred for outpatient rheumatological consultation, 142 children (42.39%) had joint pain without any objective symptoms of inflammation as their only complaint. Complaints of objective signs of arthritis (swelling of one or more joints, limited mobility in the joint, inability to support the leg, lameness, etc.) were noted in 91 patients (27.16%). No joint complaints were noted in 23 patients (6.87%), but there were various extra-articular complaints which were suspicious for the debut of rheumatic disease (13 patients had skin lesions, 5 patients had fever of unclear genesis, 3 patients had inflammatory eye diseases and 1 patient each had tics and Raynaud's phenomenon). 19 patients

Table 1. Distribution of patients by age and gender

Таблица 1. Распределение пациентов по возрасту и полу

Пациенты, n (%) / Patients, n (%)	Всего 335 (100%), из них 172 (51,34%) мужского пола (м.) / Total 335 (100%), of which 172 (51,34%) are male (m.)
Младенческого возраста (младше 1 года) / Infant age (under 1 year old)	1 (0,3%) м. (m.)
Раннего детского возраста (от 1 до 3 лет) / Early childhood (from 1 to 3 years old)	15 (4,48%), из них / of which 6 (40%) м. (m.)
Дошкольного возраста (от 3 до 7 лет) / Preschool age (from 3 to 7 years old)	67 (20%), из них / of which 41 (61,19%) м. (m.)
Младшего школьного возраста (от 7 до 12 лет) / Primary school age (from 7 to 12 years old)	129 (38,5%), из них / of which 73 (56,59%) м. (m.)
Подросткового возраста (от 12 до 18 лет) / Adolescents (from 12 to 18 years old)	123 (36,72%), из них / of which 51 (41,6%) м. (m.)

Table 2. The structure of diagnoses of referral and established diagnoses

Таблица 2. Структура диагнозов направления и установленных диагнозов

Диагнозы / Diagnoses	Диагнозы направления / Diagnoses of referral	Установленные диагнозы / Established diagnoses
M02/M13 — Артрит неуточненный, реактивный, постстрептококковый и другие постинфекционные артриты, в том числе транзиторный синовит тазобедренного сустава / Unspecified arthritis, reactive, poststreptococcal and other post-infectious arthritis arthritis, including transient synovitis of the hip joint	137 (40,9%), из них / of which 88 (64,23%) м. (m.)	115 (34,33%), из них / of which 82 (71,3%) м. (m.)
M25.5/M35.7 — Артралгии, синдром гипермобильности суставов / Arthralgia, joint hypermobility syndrome	87 (25,97%), из них / of which 39 (44,83%) м. (m.)	114 (34,03%), из них / of which 45 (39,47%) м. (m.)
M08 — Ювенильный идиопатический артрит / Juvenile idiopathic arthritis	55 (16,42%), из них / of which 16 (29,09%) м. (m.)	50 (14,93%), из них / of which 14 (28%) м. (m.)
A49.1/B95.5 — Неосложненная стрептококковая инфекция, носительство стрептококка / Uncomplicated streptococcal infection, carrier of streptococcus	24 (7,16%), из них / of which 10 (41,67%) м. (m.)	18 (5,37%), из них / of which 8 (44,44%) м. (m.)
Прочие	32 (9,55%), из них / of which 19 (59,37%) м. (m.)	38 (11,34%), из них / of which 23 (60,53%) м. (m.)

(5.67%) were referred for an outpatient consultation with a rheumatologist solely due to changes in blood tests. No clinical picture was present (17 of patients had an increase in antistreptolysin O, 1 patient — an increase in alkaline phosphatase and 1 patient — antinuclear factor).

60 patients (17.91%) did not have any complaints at the time of referral, but had a previously diagnosed musculoskeletal/connective tissue disease and were examined as part of a regular medical follow-up.

Table 2 shows a structure of the most frequent diagnoses of patients sent for rheumatology consultation as well as a structure of diagnoses established during the consultation. Other referrals include 4 patients (1.19%) with previously established orthopaedic diagnoses referred for rheumatology consultation before undergoing medical and social expert assessment (avascular necrosis of the femoral head, congenital hip dislocation, Perthes' disease, adolescent idiopathic scoliosis) as well as 4 patients (1.19%) with "erythema nodosum", 2 patients (0, 6%) with referral diagnoses of "dermatomyositis", "autoinflammatory disease" and "skin-restricted vasculitis unspecified", and 1 patient (0.3%) per "localized scleroderma", "idiopathic urticaria", "Raynaud's syndrome", "haemorrhagic vasculitis", "systemic vasculitis unspecified", "systemic lupus erythematosus", "arthritis associated with inflammatory bowel disease". In addition, 5 patients (1.49%) were referred with frankly non-specific diagnoses (superficial shin injury, heart rhythm disorder, vitiligo, allergic contact dermatitis, herpes virus infections), and 6 patients (1.79%) were referred with absurd diagnoses (M05/M06 — different variants of adult rheumatoid arthritis).

There was a fundamental discrepancy between the referral diagnosis and the diagnosis established during the consultation in 53 cases (15.82%).

Among diagnosed chronic rheumatic diseases, the vast majority were different variants of juvenile idiopathic arthritis (JIA) (50 patients). Their distribution by subtype is presented in Table 3.

Juvenile primary fibromyalgia was diagnosed in 5 patients (1.49%). 4 patients (1.19%) had unchanged previously established orthopaedic diagnoses (avascular necrosis of the femoral head, congenital hip dislocation, Perthes' disease, adolescent idiopathic scoliosis), 3 patients (0.9%) had diagnoses of "erythema nodosum" and "unspecified skin-limited vasculitis", 2 patients (0, 6%) had "autoinflammatory disease" and "Sjögren's syndrome", and 1 patient (0.3%) per "chronic recurrent multifocal osteomyelitis", "localized scleroderma", "idiopathic urticaria", "haemorrhagic vasculitis", "dermatomyositis", "Crohn's disease", "Raynaud's syndrome", "paediatric autoimmune neuropsychiatric disorder associated with infection caused by group A streptococcus". Osteoid osteoma of the femoral neck was also suspected in 1 patient (0.3%), which was subsequently excluded.

Table 3. The distribution of patients with an established diagnosis of juvenile idiopathic arthritis by subtypes of the disease

Таблица 3. Распределение пациентов с установленным диагнозом «ювенильный идиопатический артрит» по субтипам заболевания

Диагнозы / Diagnoses	Пациенты, n (%) / Patients, n (%)
Ювенильный идиопатический артрит (ЮИА), олигоартрит без поражения глаз / Oligoarticular juvenile idiopathic arthritis (JIA) without eye damage	20 (40%), из них / of which 6 (30%) м. (m.)
ЮИА, олигоартрит с поражением глаз / Oligoarticular JIA with eye damage	3 (6%), из них / of which 1 (33,33%) м. (m.)
ЮИА, полиартрит / Polyarticular JIA	3 (6%), из них / of which 0 м. (m.)
Энтезит-ассоциированный артрит / Enthesitis-related arthritis	13 (26%), из них / of which 4 (30,77%) м. (m.)
Псориатический артрит / Psoriatic arthritis	3 (6%), из них / of which 1 (33,33%) м. (m.)
Недифференцированный артрит / Undifferentiated arthritis	8 (16%), из них/ of which 2 (25%) м. (m.)

Таблица 4. Назначенная терапия

Table 4. Prescribed therapy

Назначенная терапия / Prescribed therapy	До консультации / Before the consultation	После консультации / After the consultation
НПВП местно / NSAIDs applied topically	37 (11,04%)	54 (16,12%)
НПВП внутрь / NSAIDs by mouth	117 (34,93%)	74 (22,09%)
Антибиотики / Antibiotics	44 (13,13%)	11 (3,28%)
SYSADOA	10 (2,99%)	38 (11,34%)
Метотрексат / Methotrexate	14 (4,18%)	14 (4,18%)
Азатиоприн / Azathioprine	1 (0,3%)	1 (0,3%)
Стероиды внутрь / Steroids by mouth	2 (0,6%)	2 (0,6%)
Стероиды внутримышечно / Intramuscularly steroids	4 (1,19%)	0
Стероиды внутрисуставно / Intra-articular steroids	6 (1,79%)	11 (3,28%)
Гиалуроновая кислота внутрисуставно / Intra-articular Hyaluronic acid	0	2 (0,6%)
Методы ФРМ / PRM methods	42 (12,54%)	95 (28,36%)
Без терапии / Without therapy	115 (34,33%)	126 (37,61%)

Note: NSAIDs — non-steroidal anti-inflammatory drugs; SYSADOA — Symptomatic Slow Acting Drugs for OsteoArthritis; PRM — physical and rehabilitation medicine.

Примечание: НПВП — нестероидные противовоспалительные препараты; SYSADOA — симптоматические препараты замедленного действия для лечения остеоартрита; ФРМ — физическая и реабилитационная медицина.

The remaining 10 children who consulted a rheumatologist (2.99%) were not diagnosed with any diseases.

The treatment received by patients before the rheumatologist's consultation and prescribed after the consultation is shown in Table 4.

In addition, 4 patients (1.19%) were already receiving various genetically engineered biological agents (GEBAs) by the time of consultation (2 with secukinumab and 1 per infliximab and etanercept), and were advised to continue their therapy with GEBAs further, while an additional 5 patients (1.49%) were advised to initiate it.

40 patients (11.94%) were referred for hospitalization in rheumatology department, out of which 38 children (95%) were referred for planned hospitalization, respectively 2 patients (5%) were referred for emergency hospitalization.

In 15 cases (4.48%), there was marked inadequacy of prior therapy.

1. A surgeon at a polyclinic correctly diagnosed JIA in an 8-year-old girl with long-term swelling of the knee joint, but no anti-inflammatory therapy was prescribed.
2. A 3-year-old girl with the debut of JIA with pronounced objective signs of arthritis was

treated by the orthopaedist of the polyclinic as arthralgia, and the patient received only common non-steroidal anti-inflammatory drugs (NSAIDs).

3. A 14-year-old girl with tics following a streptococcal infection was legitimately considered to have a paediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection by a outpatient clinic neurologist, but no antibiotic therapy was prescribed.
4. A paediatrician at a polyclinic diagnosed unspecified arthritis in a 10-month-old boy with swelling of the interphalangeal, knee and ankle joints and a history of psoriasis and psoriatic arthritis, but no anti-inflammatory therapy was prescribed before consultation with a rheumatologist.
5. A 7-year-old girl was referred by a paediatrician of a polyclinic with a diagnosis of erythema nodosum, but along with erythema nodosum, arthritis of the knee joint dominated the clinical picture; no NSAIDs were prescribed.
6. A 15-year-old girl with joint hypermobility syndrome was treated by a paediatrician for unspecified arthritis, and the patient received NSAIDs for a long time without effect.
7. A 10-year-old boy with streptococcal infection and arthralgias without objective signs of arthritis was treated for reactive arthritis by a paediatrician of the emergency room, and the patient received a course of NSAIDs without effect.
8. A 6-year-old boy with a rather severe onset of JIA, oligoarthritis requiring at least intra-articular steroid administration, was also diagnosed with reactive arthritis by a paediatrician of the admission department and received only NSAIDs with little or no effect.
9. A similar situation was noted in another girl of 8 years of age.
10. A 17-year-old boy with reactive arthritis who came to a rheumatologist for a follow-up appointment was initially treated for joint hypermobility syndrome, and accordingly, the patient did not receive the necessary anti-inflammatory therapy.
11. A 12-year-old girl with fibromyalgia was interpreted by a rheumatologist as JIA, and the patient received NSAIDs for a long time without any effect.

Table 5. Initial examination of patients by various specialists before referral to a rheumatologist

Таблица 5. Первичное обследование пациентов различными специалистами перед направлением к ревматологу

Специалист / Specialist	Всего пациентов / Total number of patients	Лабораторные исследования / Laboratory tests	Рентгенография / Radiography	Ультразвуковое исследование / Ultrasound examination	Расхождение диагнозов / Discrepancy of diagnoses	Неадекватность терапии / Inadequacy of therapy
Педиатр поликлиники / Pediatrician of the polyclinic	50 (24,51%)	39 (78%)	16 (32%)	12 (24%)	24 (48%)	2 (4%)
Педиатр приемного отделения / Pediatrician of the emergency department	33 (16,18%)	30 (90,91%)	32 (96,97%)	8 (24,24%)	4 (12,12%)	3 (9,09%)
Педиатр педиатрического отделения / Pediatrician of the pediatric department	9 (4,41%)	9 (100%)	7 (77,78%)	8 (88,89%)	2 (22,22%)	1 (11,11%)
Ортопед / Orthopedist	32 (15,69%)	21 (65,63%)	22 (68,75%)	16 (50%)	4 (12,5%)	1 (3,12%)
Ревматолог / Rheumatologist	54 (26,47%)	49 (90,74%)	40 (74,07%)	34 (62,96%)	7 (12,96%)	2 (3,7%)
Прочие / Others	26 (12,74%)	20 (76,92%)	2 (7,69%)	6 (23,07%)	8 (30,77%)	2 (7,69%)

12. A 10-year-old boy with widespread musculoskeletal pain, without objective signs of arthritis, was also prescribed long-term courses of NSAIDs by a rheumatologist.
13. A 12-year-old boy carrying streptococcal infection, without any complaints or objective findings on examination, was previously prescribed long-term antibiotic therapy by a rheumatologist.
14. A 15-year-old boy with a probable debut of chronic recurrent multifocal osteomyelitis was treated by a rheumatologist as arthralgia, and the patient was treated only with physical rehabilitation medicine.
15. A 2-year-old girl with JIA, oligoarthritis with high inflammatory activity, was not prescribed any additional (systemic or local injection) anti-inflammatory therapy by a rheumatologist, besides methotrexate therapy.

Among 204 patients referred to a rheumatologist for the first time, only 168 children (82.35%) had minimal laboratory tests performed, joint radiography — 119 (58.33%), joint ultrasound — 84 (41.18%). Table 5 shows the frequency of primary examination by various specialists before referral to a rheumatologist, as well as the frequency of discrepancies in diagnoses established before and after the rheumatologist's appointment and inadequate therapy by various specialists before the rheumatologist's consultation.

DISCUSSION

The structure of diagnoses and prescribed therapy almost completely coincides with the results obtained earlier based on on outpatient appointments of a rheumatologist from a St. Petersburg network of private medical centres over a period of two years [6].

Within 5 months, the majority of patients visited the rheumatologist of CDC of Children's Hospital No. 2 for the first time, most often they were referred by a paediatrician. The most frequent reason to consult a rheumatologist was joint pain without any objective symptoms of joint inflammation, while the most frequent referral diagnoses were different variants of arthritis, and the most frequent therapy was prescription of NSAIDs. A fundamental discrepancy between the referral diagnosis and the diagnosis established during the consultation, as well as the apparent inadequacy of the therapy carried out before the appointment with the rheumatologist were noted quite often. Minimally necessary laboratory tests, radiography and joint ultrasound before referral to a rheumatologist were disappointingly rare. In a publication conducted in 2021 [8], dedicated to an audit of outpatient appointments with a Moscow rheumatologist, similar results were obtained (the average age of patients was 10.4 years, 52% were boys, in 40% of cases patients were referred to a rheumatologist with suspicion of various arthritis variants, while in 57% of patients pain in one or more joints was the only complaint, preliminary laboratory and instrumental examination in accordance with modern clinical recommendations was performed only in 72% of cases). The authors note that the research revealed frequent non-compliance of outpatient doctors with the existing algorithms of examination and routing of patients. A significant proportion of patients had no objective grounds for consultation with a rheumatologist and did not receive a proper preliminary examination before consulting a specialist, which is also valid for the results of our research.

CONCLUSION

Due to the increased number of diagnosed rheumatic diseases in children, the workload of outpatient appointments of paediatric rheumatologists has significantly increased, which often leads to longer waiting times for consultations by patients in need. The situation is aggravated by a rather large percentage of non-core patients referred for rheumatology consultations (uncomplicated streptococcal infection is the most frequent, but not the only reason for unjustified referrals to rheumatologists). Moreover, referring physicians often overdiagnose (arthralgias without objective signs of joint inflammation are very rarely the only symptom of arthritis, and yet they are often interpreted in this way by paediatricians, orthopaedic traumatologists and other primary care physicians). In addition, a significant percentage of patients are referred for consultation without a minimal examination, as a result, at the initial appointment of a rheumatologist, such a patient receives referrals for tests that could have been successfully completed at the polyclinic. Patients are invited for a second appointment, which, on the one hand, additionally increases the workload of rheumatologist appointments, and on the other hand, increases the waiting time to receive appropriate specialized care. Thus, there are two possible ways out of this situation: to increase the availability

of rheumatologists in outpatient clinics and to improve the level of training in diagnosis, treatment and routing of patients with suspected rheumatic diseases among paediatricians, orthopaedic traumatologists and other specialists of polyclinics. It will reduce the proportion of referrals of non-core patients to the CDC and improve the quality of primary examination of referred patients, and, accordingly, the quality of treatment for rheumatic diseases. One of the ways to increase the availability of rheumatological care for children might be the creation of children's rheumatology offices in outpatient settings, as it is supposed to be, according to the Order N 441n dated 25 October 2012 'On Approval of the Procedure for Providing Medical Care to Children in the Profile of Rheumatology' (as amended on 21 February 2020).

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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UDC 616-053.32+616-036.81+378.147(571.62)
DOI: 10.56871/CmN-W.2024.14.88.015

PROFESSIONAL COMPETENCIES OF THE NEONATAL RESUSCITATION TEAM: LOCAL AUDIT IN MATERNITY INSTITUTIONS OF THE KHABAROVSK REGION

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For citation: Nevskaya NA, Plotonenko ZA, Senkevich OA. Professional competencies of the neonatal resuscitation team: local audit in maternity institutions of the Khabarovsk Region. Children's Medicine of the North-West. 2024;12(3):130–137. DOI: https://doi.org/10.56871/CmN-W.2024.14.88.015

Received: 17.06.2024 **Revised: 30.07.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* Providing adequate birth care remains the most important strategy for reducing neonatal mortality and morbidity. Neonatal resuscitation is crucial, as it affects early and long-term outcomes. The accumulated clinical experience demonstrates the limited possibilities of large-scale analysis of the quality of resuscitation care for newborns. In this regard, the development of effective tools for measuring and improving the quality of neonatal resuscitation is of great interest. *Goal.* To study the results of resuscitation of full-term newborns in the delivery room and the level of professional competencies of medical specialists before and after systematic training (regular simulation trainings of medical specialists) in obstetric institutions of the Khabarovsk Territory. *Materials and methods.* The study was conducted in two groups of full-term newborns born at 37 to 42 weeks of gestation, who underwent asphyxia and neonatal resuscitation in the delivery room (a solid sample), in 2017 and in 2021 — before and after the implementation of regular simulation trainings by medical specialists of maternity hospitals in the Khabarovsk Territory. The article presents an analysis of clinical and laboratory data of full-term newborns who underwent neonatal resuscitation in the delivery room, qualitative and temporal data on the implementation of neonatal resuscitation measures in the delivery room, an assessment of the professional competencies of medical specialists of obstetric institutions who underwent regular simulation retreats using specially designed scales. *Results.* All fragments of neonatal resuscitation were analyzed in a structured manner, typical disadvantages and the most difficult components to implement were identified. There was a decrease in the number of deviations from the algorithm of neonatal resuscitation in dynamics under the conditions of regular simulation re-trainings of medical specialists of obstetric institutions. *Conclusion.* The data obtained give an idea of the quality of neonatal resuscitation in practice and allow us to recommend the inclusion in the individual educational trajectory of all medical staff of obstetric institutions at any level of the educational program under the section "Neonatal resuscitation".

Keywords: *neonatal resuscitation, neonatologist, anesthesiologist-resuscitator, obstetrician-gynecologist, simulation training*

ПРОФЕССИОНАЛЬНЫЕ КОМПЕТЕНЦИИ НЕОНАТАЛЬНОЙ РЕАНИМАЦИОННОЙ БРИГАДЫ: ЛОКАЛЬНЫЙ АУДИТ В РОДОВСПОМОГАТЕЛЬНЫХ УЧРЕЖДЕНИЯХ ХАБАРОВСКОГО КРАЯ

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Для цитирования: Невская Н.А., Плотоненко З.А., Сенькевич О.А. Профессиональные компетенции неонатальной реанимационной бригады: локальный аудит в родовспомогательных учреждениях Хабаровского края // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 130–137. DOI: https://doi.org/10.56871/CmN-W.2024.14.88.015

Поступила: 17.06.2024 **Одобрена: 30.07.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение.* Предоставление надлежащей помощи при рождении остается важнейшей стратегией снижения неонатальной смертности и заболеваемости. Неонатальная реанимация имеет решающее значение, так как влияет на ранние и отдаленные исходы. Накопленный клинический опыт демонстрирует ограниченные возможности широкомасштабного анализа качества реанимационной помощи новорожденным. В связи с этим большой интерес представляет разработка эффективных инструментов измерения и улучшения качества неонатальной реанимации. *Цель*. Изучение результатов проведения реанимации доношенных новорожденных в родильном зале и уровня профессиональных компетенций медицинских специалистов до и после систематического обучения (регулярных симуляционных ретренингов медицинских специалистов) в родовспомогательных учреждениях Хабаровского края. *Материалы и методы.* Исследование проведено в двух группах доношенных новорожденных детей, родившихся на сроке от 37 до 42 недель гестации, перенесших асфиксию и неонатальную реанимацию в родильном зале (сплошная выборка), в 2017 и в 2021 году — до и после реализации регулярных симуляционных ретренингов медицинских специалистов родовспомогательных учреждений Хабаровского края. Представлен анализ клинико-лабораторных данных доношенных новорожденных, подвергшихся неонатальной реанимации в родильном зале, качественно-временных данных выполнения мероприятий неонатальной реанимации в родильном зале, оценка профессиональных компетенций медицинских специалистов родовспомогательных учреждений, проходивших регулярные симуляционные ретренинги с использованием специально разработанных шкал. *Результаты.* Структурированно проанализированы все фрагменты неонатальной реанимации, выявлены типичные недостатки и наиболее сложные для реализации компоненты. Отмечено снижение числа отклонений от алгоритма неонатальной реанимации в динамике в условиях регулярных симуляционных ретренингов медицинских специалистов родовспомогательных учреждений. *Заключение.* Полученные данные дают представление о качестве неонатальной реанимации на практике и позволяют рекомендовать включение в индивидуальную образовательную траекторию всех медицинских сотрудников родовспомогательных учреждений любого уровня образовательной программы по разделу «Неонатальная реанимация».

Ключевые слова: *неонатальная реанимация, неонатолог, анестезиолог-реаниматолог, акушер-гинеколог, симуляционное обучение*

INTRODUCTION

A neonatal period is the most vulnerable stage for child survival: this stage accounts for about half of all child deaths, with the remainder occurring before the age of five years. This trend is observed worldwide.

One in ten newborns requires neonatal resuscitation in a labor room at birth with indirect cardiac massage (ICM), 0.05% of children receive ICM combined with drug therapy (WHO, 2020).

Neonatal resuscitation in a labor room is critical to lives of neonates as it affects early and long-term outcomes [1–4, 9–11]. The complexities of neonatal resuscitation in the delivery room raise a wide range of questions, which actualizes the task of predicting the outcomes of the neonatal period, including the effectiveness of neonatal resuscitation care in a delivery room [5].

The basic principles of neonatal resuscitation care in the delivery room are the readiness of medical personnel to immediately provide resuscitative measures to a newborn and a clear algorithm of actions in the delivery room [13, 15]. In addition, the distribution of medical care at different levels of obstetric facilities (OBUs) differs, medical specialists in level II OBUs are less prepared to provide emergency care than in level III OBUs. Nevertheless, the realities of practice require a uniform level of qualification and readiness for interchangeability among all specialists.

Resuscitation care of newborns in the labor room is an emergency form of medical care, requiring special training and professional competences. The level of professionalism of medical specialists directly affects the quality of medical care.

Much experience has been accumulated, confirming the high efficiency of practice-oriented approach in mastering professional competences using simulation technologies in medicine [6–8, 12, 14, 16–20]. At the same time, the analysis of clinical simulation-training approach to mastering and maintaining competence skills for providing

medical care to newborns in the delivery room is presented non-systematically and fragmentarily.

Educational technologies make it possible to ensure the maintenance of professional competencies of medical specialists involved in the process of obstetrics. Subsequently, the quality and timeliness of resuscitative measures for newborns will positively affect the outcomes of critical conditions in neonatal resuscitation.

AIM

The aim of the research is to analyze the results of resuscitation of premature newborns in the delivery room and the level of professional competence of medical specialists before and after systematic training (regular simulation retraining of medical specialists) in obstetric institutions of Khabarovsk Territory.

MATERIALS AND METHODS

The study was performed at the Department of Pediatrics, Neonatology and Perinatology with a course of emergency medicine, on the basis of the Federal Accreditation Centre of the Federal State Budgetary Educational Institution of Higher Education 'Far Eastern State Medical University' of the Ministry of Health of the Russian Federation, as well as on the basis of obstetric institutions of Khabarovsk Territory. The research was conducted in two stages.

At the first stage, a retrospective study was carried out in a group of neonates (n=45) born in 2017 at 37 to 42 weeks of gestation. They underwent asphyxia and neonatal resuscitation in the delivery room (continuous sample), before the implementation of regular simulation retraining of medical specialists of obstetric institutions of Khabarovsk Territory.

At the second stage, a prospective study was performed in a group of neonates (n=44), born in 2021 at 37 to 42 weeks of gestation, who underwent asphyxia and neonatal resuscitation in the delivery room (continuous sample), after the implementation of regular simulation retraining of medical specialists of obstetric institutions of Khabarovsk Territory and introduction of the program on "Neonatal resuscitation and stabilization of newborns in the delivery room" into practice.

At the interim stage (2017–2021), regular simulation retraining of medical specialists of obstetric institutions of Khabarovsk Territory was implemented according to the developed "Educational program to reduce infant mortality in Khabarovsk Territory" (on the basis of the Federal Accreditation Centre of FSBEU VO FESMU of the Ministry of Health of Russia).

At each stage, clinical and laboratory data of premature newborns were examined. All neonates received neonatal resuscitation in the delivery room, qualitative and temporal data of neonatal resuscitation in the delivery room were studied, and the professional competences of medical specialists of obstetric institutions were assessed.

To assess the quality of neonatal resuscitation in the delivery room, a checklist was specially developed (based on primary medical documentation — insert card of neonatal resuscitation and stabilization in the delivery room).

An educational program on "Neonatal resuscitation and stabilization of newborns in the delivery room" (since 2017) was developed and implemented by means of simulation technologies to form and maintain the level of professional competencies of the staff of obstetric institutions; the program was implemented in the mode of regular annual retraining.

In order to assess the professional competences of the staff of obstetric facilities, interviewing was conducted with a specially designed questionnaire.

The clinical effectiveness of simulation training was assessed using specially designed scoring scales and Spearman correlation analysis.

Statistical processing of materials was carried out using application software with the help of descriptive and analytical statistics methods generally accepted in medical practice.

RESULTS

Analyzing the quality of neonatal resuscitation in the delivery room, critical components of neonatal resuscitation were identified at specific time episodes of resuscitation interventions. It was found that effectiveness and outcome of neonatal resuscitation depends on Apgar scores, lactate concentration in venous blood, and blood saturation measured by pulse oximetry.

It was found that stabilization of vital functions of the newborn increased by 1.85 times ($p < 0.05$) during neonatal resuscitation. The average time of stabilization and observation of the newborn increased 1.4 times in dynamics.

According to the assessment of neonatal status, we can conclude that in 2021, the status of the newborn was monitored more carefully, neo-

natal resuscitation measures were performed in the delivery room. The heat chain (temperature control) was observed and the effectiveness of resuscitation measures in the delivery room was dynamically assessed (Fig. 1).

According to the analysis of the interventions performed, the quality and timeliness of neonatal resuscitation interventions was 67.9% in 2017 and 97% in 2021 ($p < 0.05$).

It was demonstrated that the time of decision-making and initiation of respiratory therapy in the second group decreased by 2 times against the background of faster regression of condition severity ($p < 0.05$).

The most reliable criteria of neonatal severity are pathological changes in oxygen status indicators and an increase in blood lactate concentration.

It was found that in 2017 it was possible to reach the target oxygenation parameters only at the time interval of 5–10 minutes after birth, and in 2021 — by the 4th minute after birth ($p < 0.05$).

There was a difference in the rate of lactate normalization, which was 1.28 times faster in the second group (Table 1).

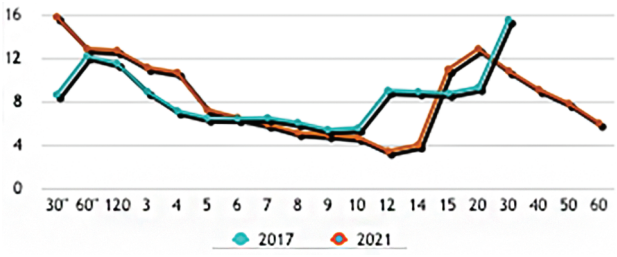

Fig. 1. Dynamics of the severity of the condition of newborns during neonatal resuscitation

Рис. 1. Динамика тяжести состояния новорожденных при проведении неонатальной реанимации

Analysis of professional competencies of medical specialists in different levels providing resuscitation care to newborns who underwent regular simulation retraining during the study period (about 80.0% of all medical specialists of obstetric institutions of Khabarovsk Territory) was conducted in each group.

100.0% of respondents expressed willingness to participate in neonatal resuscitation in the delivery room, if necessary, in 2021, compared to 58.0% of respondents in 2017.

The number of medical specialists applying neonatal resuscitation skills in their practical work increased from 76.0% in 2017 to 81.9% by 2021. 58.1% of specialists fully implement neonatal resuscitation in the delivery room, and 41.9% of specialists do not fully implement neonatal resuscitation according to the needs of a specific clinical situation.

Neonatal resuscitation in the delivery room implies teamwork, which may include all medical specialists involved in the delivery process (neonatologists, anesthesiologists-resuscitators, obstetricians-gynecologists, nurses). Participants of neonatal resuscitation teams are distributed by number: the first number — team leader, provides respiratory therapy; the second number — monitoring, indirect cardiac massage; the third number — assistant, providing vascular access, administration of drugs.

Over the analyzed period, there were performed constant simulation retraining. As a result, interchangeability, which implies team interaction with all medical specialists involved in the process of obstetrics care, increased on average by 3.7 times ($p < 0.05$) during neonatal resuscitation in the delivery room (Fig. 2).

Table 1. Characteristics of laboratory parameters of newborns who suffered asphyxia at birth

Таблица 1. Характеристики лабораторных показателей новорожденных, перенесших асфиксию при рождении

Параметры / Options	1 час после рождения / 1 hour after birth			12 часов после рождения / 12 hours after birth			24 часа после рождения / 24 hours after birth		
	2017	2021	p	2017	2021	p	2017	2021	p
pH	7,18 (±0,17)	7,15 (±0,16)	p <0,05	7,37 (±0,18)	7,38 (±0,16)	p <0,05	7,37 (±0,14)	7,45 (±0,13)	p <0,05
cGlu mmol/l	3,65 (±0,98)	3,76 (±1,23)	p <0,05	3,35 (±0,92)	4,3 (±1,05)	p <0,05	6 (±0,81)	3,9 (±0,98)	p <0,05
cLac mmol/l	6,24 (±3,53)	6,68 (±3,25)	p <0,05	3,5 (±3,34)	2,75 (±3,18)	p <0,05	1,8 (±2,98)	1 (±2,87)	p <0,05
cBase(Ecf) mmol/l	–9,09 (±5,36)	–10,15 (±4,71)	p <0,05	–0,31 (±5,17)	–1,5 (±4,89)	p <0,05	–0,5 (±5,02)	1,9 (±4,78)	p <0,05

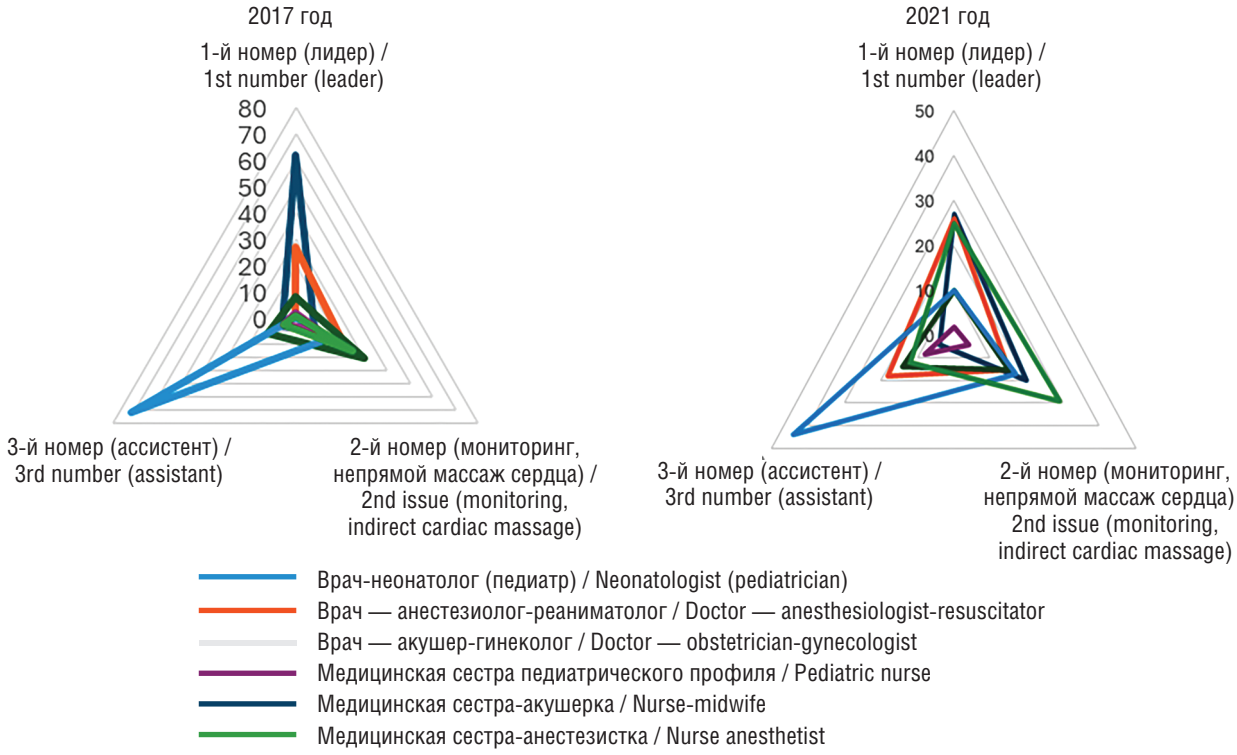

Fig. 2. Distribution in team work in neonatal intensive care in the delivery room of doctors and nursing staff of obstetric institutions in 2017 and 2021

Рис. 2. Распределение в командной работе в неонатальной реанимации в родильном зале врачей и среднего медицинского персонала родовспомогательных учреждений в 2017 и 2021 гг.

A reliable expansion of professional competences among obstetrics specialists was revealed in the course of regular professional simulation retraining.

The clinical effectiveness of simulation training of medical specialists of obstetric institutions was analyzed. Using specially developed scales, evidence of clinical effectiveness of simulation training was obtained. The correlation between the dynamics of clinical changes in the state of newborns during neonatal resuscitation depending on the resuscitation measures performed was revealed. The interventions were performed by medical specialists of obstetric institutions who underwent regular simulation retraining during the study period.

Key time episodes of neonatal resuscitation in the labor room were identified, during which the quality of neonatal resuscitation components in the labor room critically influenced the regression of the severity of the condition.

Correlation analysis using the Spearman correlation criterion in the first group of newborns revealed a relationship between the severity of the condition and the quality of care during the entire period of neonatal resuscitation in the labor room. At the same time, there are reliable features in the significance of the components of resuscitation measures for newborns in the labor room at certain time episodes.

The greatest contribution to the dynamics of clinical changes was made by neonatal resuscitation measures performed in the first minutes of life ($p < 0.05$) and at the 15th and 30th minutes of stabilization ($p < 0.05$).

Thus, assessment of the newborn's condition at the 30th second, 1st and 2nd minutes ($r = 0.557$, 0.755 and 0.598) has priority importance. The clinical scenario that unfolds depends on the assessment as well. The next important quality of neonatal assessment is the 12th, 14th and 15th minutes ($r = 0.095$). The most important component is the provision of heat chain during the first 5 minutes of life ($r = 0.786$, 0.315, 0.309).

The severity of the condition resolves with timely measures to ensure airway patency, it depends on the selected parameters of respiratory support within the period of 1st and 2nd minute ($r = 0,38$, 0,442) as well as on the speed of decision making related to tracheal intubation and transfer to artificial lung ventilation.

CONCLUSION

Introduction of an educational program for specialists of obstetric institutions on the section "Neonatal resuscitation and stabilization of newborns in the delivery room" allowed:

- to reduce the time of decision-making and initiation of respiratory therapy by 2 times against the background of faster regression of the severity of the condition of newborns ($p < 0.05$);
- to increase timely stabilization of vital functions of newborns in the delivery room by 1.85 times ($p < 0.05$);
- to significantly expand the range of professional competences of the staff of obstetric institutions providing medical care to newborns ($p < 0.05$);
- to increase interchangeability in teamwork during resuscitation in the delivery room by 3.7 times ($p < 0.05$);
- to increase the adherence to neonatal resuscitation algorithms on 77.2 to 93% ($p < 0.05$).

The findings demonstrate faster stabilization of neonates who received better neonatal resuscitation in the delivery room.

Thus, the data obtained allow us to recommend the inclusion of the educational program on "Neonatal resuscitation and stabilization of newborns in the delivery room", which has proven its clinical effectiveness, in the individual educational trajectory of all medical staff of obstetric institutions at any level.

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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ISSN 2221-2582

UDC 616.127+616.831-005.4-053.7+617.754.5-031.41
DOI: 10.56871/CmN-W.2024.71.47.016

ISOLATED VISUAL FIELD IMPAIRMENT IN REPEATED CEREBRAL CIRCULATORY DISORDERS IN THE BASIN OF THE POSTERIOR CEREBRAL ARTERY IN A TEENAGER

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For citation: Tadtayeva ZG, Galustyan AN, Zavialov VO, Shanina ES, Iskalieva AR, Sardaryan IS. Isolated visual field impairment in repeated cerebral circulatory disorders in the basin of the posterior cerebral artery in a teenager. Children's Medicine of the North-West. 2024;12(3):138–145. DOI: https://doi.org/10.56871/CmN-W.2024.71.47.016

Received: 02.07.2024 **Revised: 20.08.2024** **Accepted: 10.09.2024**

Abstract. Ischemic stroke in the basin of the posterior cerebral artery (PCA) is a rare disease. The clinical observation of repeated episodes of ischemic stroke in a 16-year-old patient in the PCA basin, manifested by isolated visual disturbances (visual field defects) and headache, is presented. The disease debuted with visual flicker. 6 months after the disease, incomplete homonymous hemianopia developed — lower quadrant hemianopi, confirmed by computer perimetry. When performing magnetic resonance imaging (MRI) of the brain, foci of ischemic changes in the left parietal-occipital region regione were revealed. Partial restoration of visual functions was noted against the background of therapy. The presence of isolated homonymous hemianopia dictates the need for highly informative diagnostic methods including magnetic resonance imaging of the brain and perimetric examination for timely diagnosis, adequate therapy and prevention of the disease.

Keywords: *vertebrobasilar pool, posterior cerebral stroke, homonymous hemianopia, lower quadrant hemianopia, children*

ИЗОЛИРОВАННОЕ НАРУШЕНИЕ ПОЛЕЙ ЗРЕНИЯ ПРИ ПОВТОРНЫХ НАРУШЕНИЯХ МОЗГОВОГО КРОВООБРАЩЕНИЯ В БАССЕЙНЕ ЗАДНЕЙ МОЗГОВОЙ АРТЕРИИ У ПОДРОСТКА

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Для цитирования: Тадтаева З.Г., Галустян А.Н., Завьялов В.О., Шанина Е.С., Искалиева А.Р., Сардарян И.С. Изолированное нарушение полей зрения при повторных нарушениях мозгового кровообращения в бассейне задней мозговой артерии у подростка // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 138–145. DOI: https://doi.org/10.56871/CmN-W.2024.71.47.016

Поступила: 02.07.2024 **Одобрена: 20.08.2024** **Принята к печати: 10.09.2024**

Резюме. Ишемический инсульт в бассейне задней мозговой артерии (ЗМА) является редким заболеванием. Приведено клиническое наблюдение повторных эпизодов ишемического инсульта у пациента 16 лет в бассейне ЗМА, проявившегося изолированными зрительными нарушениями (дефектами поля зрения) и головной болью. Заболевание дебютировало зрительным мерцанием. Через 6 месяцев после болезни

развилась неполная гомонимная гемианопсия — нижнеквадрантная гемианопсия, подтвержденная компьютерной периметрией. При выполнении магнитно-резонансной томографии (МРТ) головного мозга выявлены очаги ишемических изменений в левой теменно-затылочной области. На фоне терапии отмечено частичное восстановление зрительных функций. Наличие изолированной гомонимной гемианопсии диктует необходимость проведения высокоинформативных методов диагностики с включением МРТ головного мозга и периметрического обследования для своевременной диагностики, адекватной терапии и профилактики заболевания.

Ключевые слова*: вертебробазилярный бассейн, задний мозговой инсульт, гомонимная гемианопсия, нижнеквадрантная гемианопсия, дети*

INTRODUCTION

Strokes in children and adolescents constitute an urgent medical and social problem. The incidence of an arterial ischemic stroke in childhood ranges from 1.2 to 13 cases per 100,000 [1, 2]. Epidemiologic studies show that about 10–30% of all ischemic strokes and transient ischemic attacks occur in the vertebrobasilar basin (VBB) [3, 4]. Blood flow disorders in the posterior cerebral artery (PCA) blood supply zone occur in only 5–10% of cases. Despite secondary prevention with antiaggregants, recurrent cerebrovascular episodes in the VBB are not uncommon and occur in 23–52% of children [5] during the first three years.

Clinical diagnosis of insufficient blood supply to the VBB is difficult because of cross-supply of the vascular basins, so the clinical picture within the brain stem and posterior hemispheres of the brain may be transient and/or masked by other diseases [6].

The symptom complex of stroke in the VBB is characterized by a severe course: depression of consciousness of varying severity, ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficits, systemic dizziness, ataxia, dysarthria, headache, nausea, vomiting, and nystagmus [7–9]. 45–67% of patients develop persistent visual field impairment in the acute period of stroke, which fully recovers within the first 6 months of stroke in 7.5% of patients [10].

Ischemic stroke in the VBB occurs when blood flow is impaired in the vertebral, basilar, and posterior cerebral arteries. The vertebral arteries are divided into 4 segments (V_1–V_4), the first three of which form the extracranial portion and V_4 comes from the intracranial portion. The bilateral segments of V_4 merge to form the basilar artery. The cerebellar arteries (superior, anterior inferior, and posterior inferior) are part of the VBB and participate in the blood supply to the cerebellum. The two posterior cerebral arteries (PCA) supply blood to the cortical areas in the region of sulcus spinous, and the optic radiation in some cases receives blood from branches of the middle cerebral artery; accordingly, homonymous hemianopsia does not always imply infarction in the PCA basin [11, 12]. Most of the visual cortex is supplied with blood by branches of the PCA, additionally in the region of the occipital pole by branches of the middle cerebral artery (MCA) [13].

Ischemic stroke in the PCA basin in childhood is poorly studied. The most frequent variant of visual field changes is homonymous hemianopsia, occurring in 75% of patients. PCA occlusion is manifested by visual field defects: contralateral homonymous hemianopsia or contralateral quadrant hemianopsia (lower quadrant hemianopsia in the case of wedge lesions or upper quadrant hemianopsia in the case of lingual gyrus lesions) [12, 14, 15] in the absence of other manifestations of neurologic deficit. The literature describes cases of stroke in the PCA, which are manifested by hallucinations by the mechanism of "cortical release", visual and color agnosia, prosopagnosia, blindness denial syndrome (Anton's syndrome), visual attention deficit and optic-motor agnosia (Balint's syndrome) [10, 11].

We present a rare clinical observation of a patient with recurrent ischemic stroke in the PCA basin, which manifested an isolated visual field disorder in the form of incomplete homonymous hemianopsia — lower quadrant hemianopsia.

CLINICAL OBSERVATION

Patient A., 16 years old, came to the emergency room of the hospital with complaints of visual disturbance (partial loss of visual fields). From the anamnesis it is known that the disease developed acutely with visual disturbance (loss of the right visual fields) and subsequent marked diffuse headache without nausea and vomiting. He was urgently hospitalized in the neurosurgical department with the diagnosis: acute cerebral circula-

 ISSN 2221-2582

tion disorder of ischemic type in the VBB. The first symptoms of the disease appeared 6 months before admission to the hospital in the form of visual flickering lasting 10–15 minutes. The frequency of visual disturbances in dynamics increased from once a month to daily. In 6 months from the onset of the disease, visual field loss on the left side developed, which regressed almost completely within 10 days. Repeated cerebral circulation disorder occurred 27 days after the first acute vascular episode in the form of loss of visual fields on the right and headache, in connection with which he was urgently hospitalized.

Anamnesis of life. Obstetric history is aggravated (acute respiratory disease and threat of early termination). He was born on time against the background of mild preeclampsia. Birth weight — 3700 g, height — 53 cm, Apgar score — 8/9 points. He was discharged on time. Psychomotor development corresponded to the age. He was observed by a neurologist at preschool and primary school age for compulsive movements, tic hyperkinesis. During his life he suffered from acute respiratory viral infections, bronchitis, infectious mononucleosis, chickenpox. Suffers from vitiligo. He denies traumas, convulsions, loss of consciousness. Heredity: paternal grandmother had a stroke at the age of 50, peptic ulcer disease. Paternal hypertension in the grandfather. Somatic status at admission: condition of average severity. Height 168 cm, weight 58 kg. Skin and visible mucous membranes with no rush. Turgor and elasticity of tissues are preserved. Nasal breathing is free. Breathing is conducted in all sections, vesicular, no rales. Frequency of respiratory movements — 18 per minute. Heart tones are rhythmic. Blood pressure (BP) 125/70 mm Hg, heart rate (HR) — 104 per minute, respiratory rate — 20 per minute. The abdomen is soft, painless. Stool, urination is normal.

Neurologic status. Consciousness is clear. Active, available for contact, adequately responds to examination. Olfaction is not disturbed. Eye slits D=S. Pupils D=S. Photoreaction is alive. Eye movements are not limited, there is no nystagmus. Convergence, accommodation are not disturbed. No diplopia. The trigeminal nerve exit points are painless. Sensitivity on the face is preserved. Nasolabial folds are equal. Hearing is not disturbed. Tongue on the center line. Swallowing and phonation are intact. Speech is clear. Movements are complete in the extremities. No paresis. Muscle tone is not disturbed. Hand reflexes are alive, D=S, knee reflexes are alive, Achilles reflexes are alive. Abdominal reflexes are alive, symmetrical. There are no pathologic reflexes. Coordination tests is performed satisfactorily. There are no meningeal symptoms.

Laboratory admission tests

Clinical blood analysis: increase in hemoglobin — 169 g/L, leukocytes — 12.3×10^9/L, monocytes — 0.88×10^9/L, average concentration of hemoglobin in erythrocytes — 363 g/L, increase in the average volume of platelets — 11.1 fL, increase in the distribution width of erythrocytes — 14.7%; biochemical analysis of blood (including lipoprotein levels), urinalysis within normal limits.

Enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) of blood to viruses of *Herpes viridae* did not reveal the presence of viruses.

Coagulation tests (activated partial thromboplastin time (APTT), prothrombin index (PTI), prothrombin time (PTT), fibrinogen) within normal limits.

Blood homocysteine — 8.3 mmol/L.

Blood: antiphospholipid syndrome — negative result.

Examination of ophthalmologist: optic disc is pale pink, borders are clear, scleral myopic cones on the temporal side, vessels of normal course and caliber, there is no pathology in the macular area and in the periphery in the visible area. Myopia of medium degree: OD: 0.5; sph –4.50 = 1.0;

OS: 0.4; sph –4.50 = 1.0. Computerized perimetry: homonymous lower quadrant hemianopsia (Fig. 1).

Electroencephalography (EEG): no focal changes, no paroxysmal forms of activity were detected.

MRI examination of the brain revealed foci of ischemia in the occipital region on both sides (Figs. 2, 3).

MR angiography: hypoplasia of the V_5 segment of the right vertebral artery.

Multispiral computed tomography (MSCT) of the brain and neck with contrast: CT picture of thrombosis of the left vertebral artery (V_1–V_2 segments).

Against the background of antiaggregant and anticoagulant therapy under the control of coagulation tests, the patient's condition stabilized. Positive dynamics in the form of partial recovery of visual functions and laboratory parameters were noted.

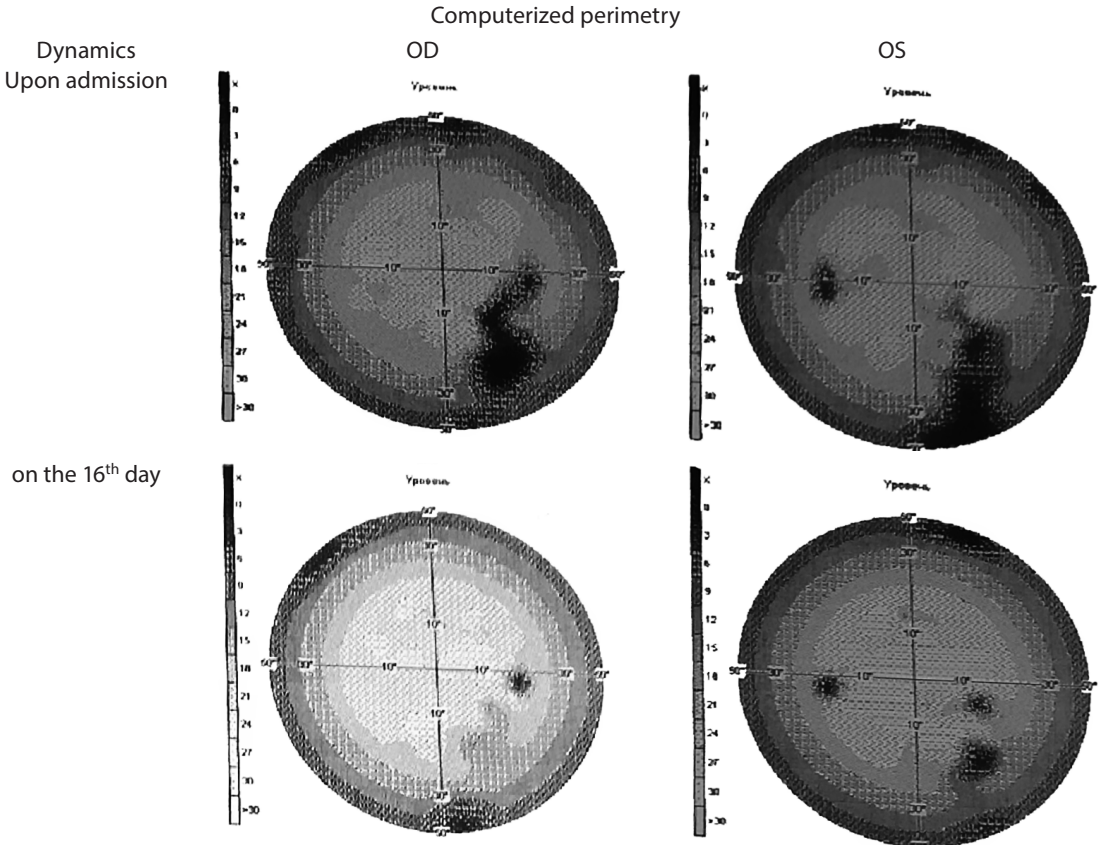

Fig. 1. Right-sided lower-quadrant homonymous hemianopia on the computer perimeter in dynamics

Рис. 1. Правосторонняя нижнеквадрантная гомонимная гемианопсия на компьютерном периметре в динамике

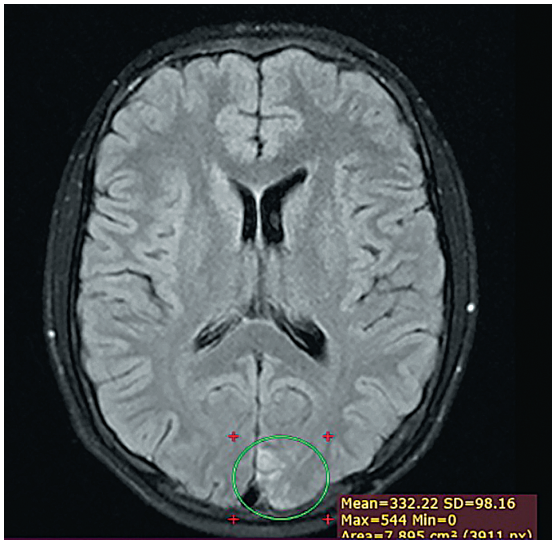

Fig. 2. MRI of the brain of a 16-year-old patient with foci of ischemic changes in the left occipital lobe

Рис. 2. МРТ головного мозга пациента 16 лет с очагами ишемических изменений в левой затылочной доле

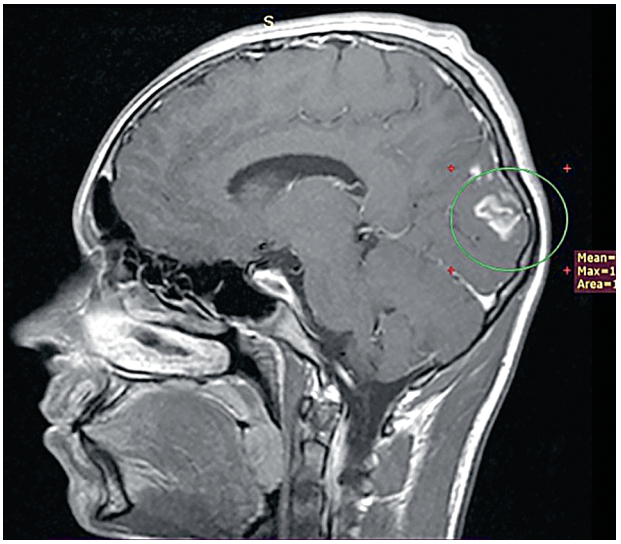

Fig. 3. MRI of the brain of a 16-year-old patient with foci of ischemic changes in the left parietal region

Рис. 3. МРТ головного мозга пациента 16 лет с очагами ишемических изменений в левой теменной области

 ISSN 2221-2582

A genetic panel of thrombophilia was performed in outpatient conditions. Allelic polymorphism of genes was revealed:

- *MTR 2756* methionine synthase gene (*Asp 919 Glu*), heterozygote A/G;
- methionine synthase reductase gene *MTRR 66 A/G,* heterozygote A/G ;
- methylenetetrahydrofolate reductase gene *MTHFR 677 C/T (Ala 222 Val)*, heterozygote C/T;
- platelet integrin subunit IIIA gene (platelet fibrinogen receptor) *ITGBZ 1565 T/C*, heterozygote T/C;
- platelet receptor gene for collagen (integrin alpha-2) *ITGA 807 C/T,* heterozygote C/T .

DISCUSSION

The diagnosis of ischemic stroke in the PCA basin is difficult because of the peculiarities of the circulation and lack of symptoms specificity [16]. The most frequent manifestations of the disease are homonymous visual field disturbances and headache. The nonspecific nature of symptoms necessitates differential diagnosis with migraine, acute sinusitis, and multiple sclerosis. The disease debuted with flickering vision without headache, which was ignored by the patient for quite a long time, leading to late diagnosis and treatment. The flickering vision was not accompanied by headache and indicated hemodynamic disorders of the visual system on one side above the chiasma. The patient was admitted to the hospital with partial loss of the same visual fields, which is a sign of blood flow disturbance in the area of the striatal cortex, optic radiation or lateral patellar body [17, 18]. Ischemic changes detected on neuroimaging in the parieto-occipital region confirm the level of visual pathway damage.

CT angiography of the spine diagnosed thrombosis of the left vertebral artery (V_1–V_2 segments). It is known that occlusion of a single vertebral artery does not lead to ischemic infarction; however, if the patient has cerebral infarction in the basin of PCA branches and vertebral artery thrombosis, the causal relationship is more likely in combination with pathology in the cervical spine, craniovertebral region, presence of cervical rib, vascular atherosclerosis, and Willis Circle anomalies. Cervical carotid and vertebral artery dissection is a well-known cause of stroke in young adults, especially in patients with migraine, fibromuscular dysplasia, hypertension, and trauma [19, 20].

Stroke in childhood and adolescence is rarely associated with adult obligatory risk factors such as vascular atherosclerosis, arterial hypertension, dyslipidemia, diabetes mellitus, etc. The main etiologic and predisposing factors are recognized as acquired and congenital prothrombotic disorders involving heart diseases (including congenital malformations and cardiomyopathies), (arteriopathies craniocervical arterial dissection, fibromuscular dysplasia, primary angiitis); congenital metabolic disorders; infections; head and neck trauma; sickle cell anemia; prothrombotic disorders; autoimmune diseases and malignancies [21, 22]. The most significant factors are heart defects, arteriopathies, hereditary thrombophilia, and prothrombotic disorders [23]. The factors determining the risk of stroke recurrence are not fully understood. They include heart disease, arteriopathies, prothrombotic factors, monogenic forms of stroke, and hereditary thrombophilia due to polymorphisms of genes of blood coagulation factors, fibrinolysis, thrombocyte hemostasis, and homocysteine metabolism [24].

In our observation, the patient had a combination of five polymorphisms of genes related to the hemostasis system: heterozygous mutations of *MTHFR* and platelet glycoprotein genes, i.e. there is a polygenic hereditary predisposition to thrombotic lesions of cerebral vessels [25].

Mutation in the methylenetetrahydrofolate reductase (MTHFR) gene leads to a thermolabile enzyme with reduced enzymatic activity and is one of the reasons for the development of hyperhomocysteinemia (HHC) [26]. Studies have shown that genetically determined HHC is associated with an increased risk of ischemic stroke due to its effects on the endothelium of the vascular wall not only in adults but also in children [27]. The patient's plasma homocysteine level was 8.3 μmol/L (with a normal range of 5 μmol/L in children) [28].

Disturbance in the system of vascular-platelet hemostasis is one of the significant pathophysiologic causes of stroke development regardless of etiology. Polymorphisms of platelet glycoprotein receptors, called human platelet antigens (HPA), modulate receptor density, altering platelet function and thrombus formation [29]. Particular attention has been paid to the fibrinogen receptor, GpIIb/IIIa complex, which mediates aggregation of active platelet forms. The pathogenetic role of GpIIIa 1565 T/C glycoprotein polymorphism is due to the increased receptor function of platelets and aggregation of these blood platelets, and fibrinogen is the main plasma cofactor of this process. An almost threefold increased risk in HPA carri-

ers for venous sinus thrombosis in children has been found [30]. Carriage of several polymorphic thrombophilia factors in a patient may indicate a cumulative prothrombotic effect on the risk of ischemic stroke [31, 32]. Thus, one of the risk factors for stroke development in a patient is hereditary multigenic thrombophilia.

DISCUSSION

The sudden onset of homonymous visual field defects is a consequence of cerebral vascular lesions in the occipital lobe supplied by branches of the posterior cerebral artery. Thorough clinical examination involving neuroimaging and perimetry makes it possible to diagnose a stroke in the basin of the posterior cerebral artery branches, and to provide timely adequate therapy and secondary prevention to avoid recurrence [33].

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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ISSN 2221-2582

UDC 616-053.32+612.648+615.816.2+616.24-008.4-073.96
DOI: 10.56871/CmN-W.2024.75.32.017

NON-INVASIVE NAVA AS AN INITIAL METHOD OF ARTIFICIAL VENTILATION IN A PREMATURE NEWBORN WITH EXTREMELY LOW BIRTH WEIGHT. CLINICAL CASE

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For citation: Anurev AM, Gorbachev VI. Non-invasive NAVA as an initial method of artificial ventilation in a premature newborn with extremely low birth weight. Clinical case. Children's Medicine of the North-West. 2024;12(3):146–151. DOI: https://doi.org/10.56871/CmN-W.2024.75.32.017

Received: 07.06.2024 **Revised: 17.07.2024** **Accepted: 10.09.2024**

Abstract. Optimal respiratory support in newborns with critical body weight is one of the priorities in providing quality medical care. Currently, the criteria for effective ventilation are not only a stable level of saturation and reference values of blood gas composition, but also maintaining a balance between the proposed respiratory support and the respiratory needs of the child. In addition, a very important condition for protective ventilation in these patients is minimizing mechanical impact, which plays a key role in the development of ventilator-induced lung damage and bronchopulmonary dysplasia. In this regard, approaches to initial respiratory support must be not only justified, but also safe. A clinical case of the successful use of non-invasive NAVA ventilation as a starting method of respiratory support in premature newborns with a birth weight of 660 g is presented. The parameters of focal echocardiography are analyzed; the dynamics of X-ray images and blood gas parameters are presented. The influence of this regimen on the efficiency of spontaneous breathing and the general condition of the child was assessed.

Keywords: *premature newborns, NAVA ventilation, extremely low birth weight, focal echocardiography, non-invasive ventilation*

НЕИНВАЗИВНАЯ NAVA В КАЧЕСТВЕ СТАРТОВОГО МЕТОДА ИСКУССТВЕННОЙ ВЕНТИЛЯЦИИ ЛЕГКИХ У НЕДОНОШЕННОГО НОВОРОЖДЕННОГО С ЭКСТРЕМАЛЬНО НИЗКОЙ МАССОЙ ТЕЛА ПРИ РОЖДЕНИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Для цитирования: Анурьев А.М., Горбачев В.И. Неинвазивная NAVA в качестве стартового метода искусственной вентиляции легких у недоношенного новорожденного с экстремально низкой массой тела при рождении. Клинический случай // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 146–151. DOI: https://doi.org/10.56871/CmN-W.2024.75.32.017

Поступила: 07.06.2024 **Одобрена: 17.07.2024** **Принята к печати: 10.09.2024**

Резюме. Оптимальная респираторная поддержка у новорожденных с критической массой тела — одна из приоритетных задач при оказании качественной медицинской помощи. В настоящее время критериями эффективной вентиляции являются не только устойчивый уровень сатурации и референсные значения газового состава крови, но и сохранение баланса между предложенной респираторной поддержкой и дыхательными потребностями ребенка. Кроме того, немаловажным условием протективной вентиляции у данных пациентов является минимизация механического воздействия, которое играет ключевую роль

в развитии вентилятор-индуцированного повреждения легких и бронхолегочной дисплазии. В связи с этим подходы к стартовой респираторной поддержке должны быть не только обоснованными, но и безопасными. Представлен клинический случай успешного применения неинвазивной нервно-регулируемой вентиляции легких (NAVA-вентиляции) в качестве стартового метода респираторной поддержки у недоношенного ребенка с массой тела при рождении 660 г. Проанализированы параметры фокусной эхокардиографии, представлена динамика рентгенологических снимков и показателей газового состава крови. Оценено влияние данного режима на эффективность спонтанного дыхания и общее состояние ребенка.

Ключевые слова: *недоношенные новорожденные, NAVA-вентиляция, экстремально низкая масса тела при рождении, фокусная эхокардиография, неинвазивная вентиляция легких*

INTRODUCTION

Использование современных стратегий проведThe use of modern strategies of artificial lung ventilation (ALV) in preterm neonates has led to an increase in their survival rate. However, the high incidence of bronchopulmonary dysplasia and ventilator-induced damage makes the problem of choosing the optimal mode and parameters of ALV extremely urgent [1].

One of the "sparing" methods is Volume Guarantee Ventilation, which is increasingly used in neonatology. It is adaptive ventilation that uses complex computer algorithms to provide patients with a given respiratory volume [2]. It can reduce lung damage involving the precise delivery of a set respiratory volume [3]. Volume Guarantee ventilation is different from traditional volume-controlled ventilation. During VG ventilation, airflow is used to provide a set respiratory volume, whereas ventilation control is pressure-based. In modern ventilators, respiratory volume measurement is made possible through the use of a proximal flow sensor. It allows to control the respiratory volume and to correct ventilation parameters in time, thus minimizing the risks of lung volumetric injury [4].

Another modern strategy of respiratory support in preterm infants is the use of neurally regulated ventilation, which uses the electrical signal of the diaphragm as a trigger for the initiation of a machine breath [5]. J. Beck showed that Neurally Adjusted Ventilatory Assist (NAVA-ventilation) is a kind of respiratory prosthesis, where the diaphragm and the ventilator equally support breathing and provide respiratory support not only synchronously, but also in proportion to the patient's needs [6]. Studies performed by a group of authors led by M. Wu, also demonstrated qualitative interaction between the patient and ventilator in NAVA mode, both in adults and children [7].

Preterm newborns, especially those with very low and extremely low birth weight, are highly sensitive to changes in intrathoracic pressure and respiratory volume fluctuations, so the choice of ventilator mode should be reasonable and effective [8]. Methodological recommendations for the management of newborns with respiratory distress syndrome do not provide a specific mode of ventilatory support, which makes it possible for a resuscitator or neonatologist to take a non-standard approach to the choice of respiratory support. That is why we would like to present a clinical case of using non-invasive NAVA ventilation in a baby with a body weight of 660 g as a starting mode of ventilation.

AIM

To evaluate the efficacy of non-invasive NAVA ventilation as a starting method of respiratory therapy in a premature neonate with a birth weight of 660 g.

MATERIALS AND METHODS

During the course of the research there have been analyzed: resuscitation card, observation sheets, which included heart rate, blood pressure and saturation indices, diuresis rate. In addition, X-rays, neurosonography and echocardiography were analyzed. The dynamics of changes in blood gas composition and electrical activity of the diaphragm assessed by graphic monitoring in NAVA mode is also presented.

Within the framework of focal echocardiography, myocardial preload was evaluated to exclude hypovolemia and fluid overload, myocardial contractility and cardiac afterload [9]. Myocardial contractility was determined by ejection fraction and shortening fraction, afterload — by measuring left ventricular wall stress (ESWS — end systolic wall stress) during systole using the formula:

$$ESWS\ (\frac{г}{см^2}) = 1{,}35 \cdot АД\ ср \cdot \frac{КСР}{4 \cdot ТЗСЛЖ\ с \cdot (1 + ТЗСЛЖ\ с/КСР)}.$$

In addition, open ductus arteriosus was diagnosed, its diameter and significance for systemic and cerebral blood flow were determined.

ISSN 2221-2582

CLINICAL CASE

Child P., date of birth 19.12.2023. Birth weight 660 g, height 30 cm, Apgar score 6–7 points, boy. Obstetric diagnosis of the mother: premature delivery by cesarean section at 28 weeks. Intrauterine fetal hypoxia before delivery. Insufficient fetal growth. Scar on the uterus. Chronic nicotine addiction. Candida vaginitis. Laparotomy. Caesarean section according to Gusakov. From the history of the mother, it is known that the present pregnancy is the 6th, delivery is the 2nd. Has one healthy child of eleven years old. Natural miscarriages in 2014, 2016, 2019 and 2020. Registered at the antenatal clinic for the last pregnancy in the last 8 weeks. At 15 weeks there was a suspicion of fetal genetic abnormality, but the diagnosis was not confirmed by chorionbiopsy. From the 21st week onward, there was delayed fetal growth, amniotic masses in the uterine cavity, and uteroplacental blood flow abnormalities. Uterine and fetoplacental blood flow disorders at 26 weeks. At 27 weeks, the mother had an acute viral infection.

On 19.12.2023 at the term of 28 weeks and 3 days a boy was born by cesarean section. At birth, the condition was severe, due to respiratory failure, deep immaturity. From the first minutes respiratory support was carried out in the form of non-invasive ventilation with positive pressure at the end of exhalation, followed by transition to nasal ventilation with intermittent positive pressure. Taking into account the persisting oxygen demand of 60% at the 10th minute, noninvasive administration of surfactant preparation 200 mg/kg was performed. A peripheral venous catheter was placed, infusion therapy was started, and colostrum was given. By the 30th minute, the neonate was stabilized in a heat-saving film in a transport cuvette on noninvasive ventilation in the mode of nasal ventilation with intermittent positive pressure, he was transported to the intensive care unit N 7 of the Irkutsk Regional Perinatal Center.

Upon admission to the intensive care unit, the child was examined: review chest radiography,

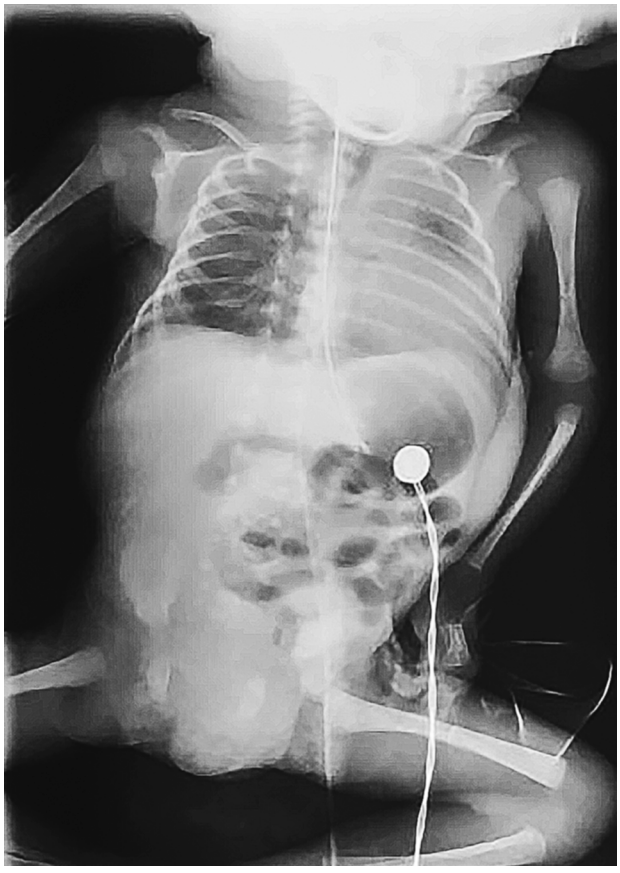

Fig. 1. X-ray of the chest organs in the first hour of life

Рис. 1. Рентгенография окружности грудной клетки, выполненная в первый час жизни

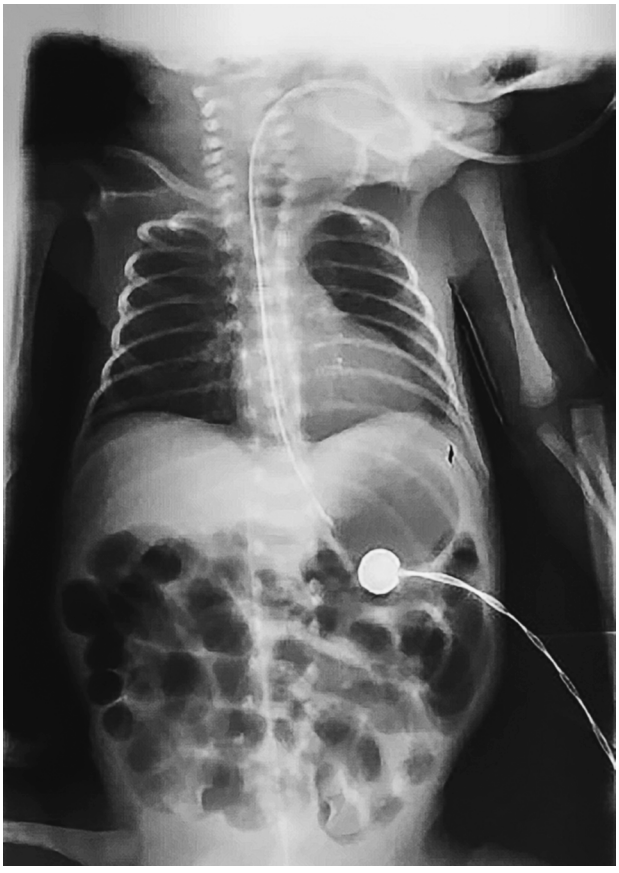

Fig. 2. X-ray of the chest organs. Dynamics after 6 hours from the moment of birth

Рис. 2. Рентгенография окружности грудной клетки. Динамика через 6 часов с момента рождения

Table 1. Hemodynamic profile according to focal echocardiographic

Таблица 1. Гемодинамический профиль по данным фокусной эхокардиографии

Сутки / Day	Объемный кровоток в легочной артерии (мл/кг в минуту) / Volumetric blood flow in the pulmonary artery (ml/kg per minute)	d ОАП (мм) / d DA (mm)	LA/Ao	Ri ПМА / Ri ACA	ФВ ЛЖ (%) / EF LV (%)	ФУ ЛЖ (%) / FS LV (%)	ESWS гр/см^2 / g/cm^2
1	435	0,2	1,33	1,0	77,8	40,9	28
2	372	0,18	1,2	0,79	72,5	38,9	38
3	305	0,1	1,1	0,76	76,5	41,3	35
4	288	–	1,1	0,75	77,4	41,9	37

Note: DA — ductus arteriosus; ACA — anterior cerebral artery; EF LF — ejection fraction left ventricular; FS LV — fractional shortening left ventricular.

Примечание: ОАП — открытый артериальный проток; ПМА — передняя мозговая артерия, ФВ ЛЖ — фракция выброса левого желудочка, ФУ ЛЖ – фракция укорочения левого желудочка.

Table 2. The blood gas parameters in the first 3 days

Таблица 2. Показатели газового состава крови в первые трое суток

Сутки / Day	pH	pCO_2	pO_2,	BE	HCO_3	Лактат / Lactate
1	7,29 [7,14; 7,35]	46,1 [37,6; 53,3]	40,5 [30,3; 53,9]	–4,2 [–9,4; +1,5]	20,3 [16,1; 24,2]	2,2 [1,7; 2,6]
2	7,33 [7,22; 7,37]	43,2 [33,6; 48,9]	38,6 [33,2; 51,1]	–3,1 [-5,4; +0,3]	21,1 [17,5; 23,0]	1,9 [1,2; 2,0]
3	7,31 [7,21; 7,39]	41,0 [32,5; 46,0]	39,4 [32,9; 48,8]	–4,0 [–7,8; –1,1]	20,7 [16,8; 21,9]	2,1 [1,0; 2,3]

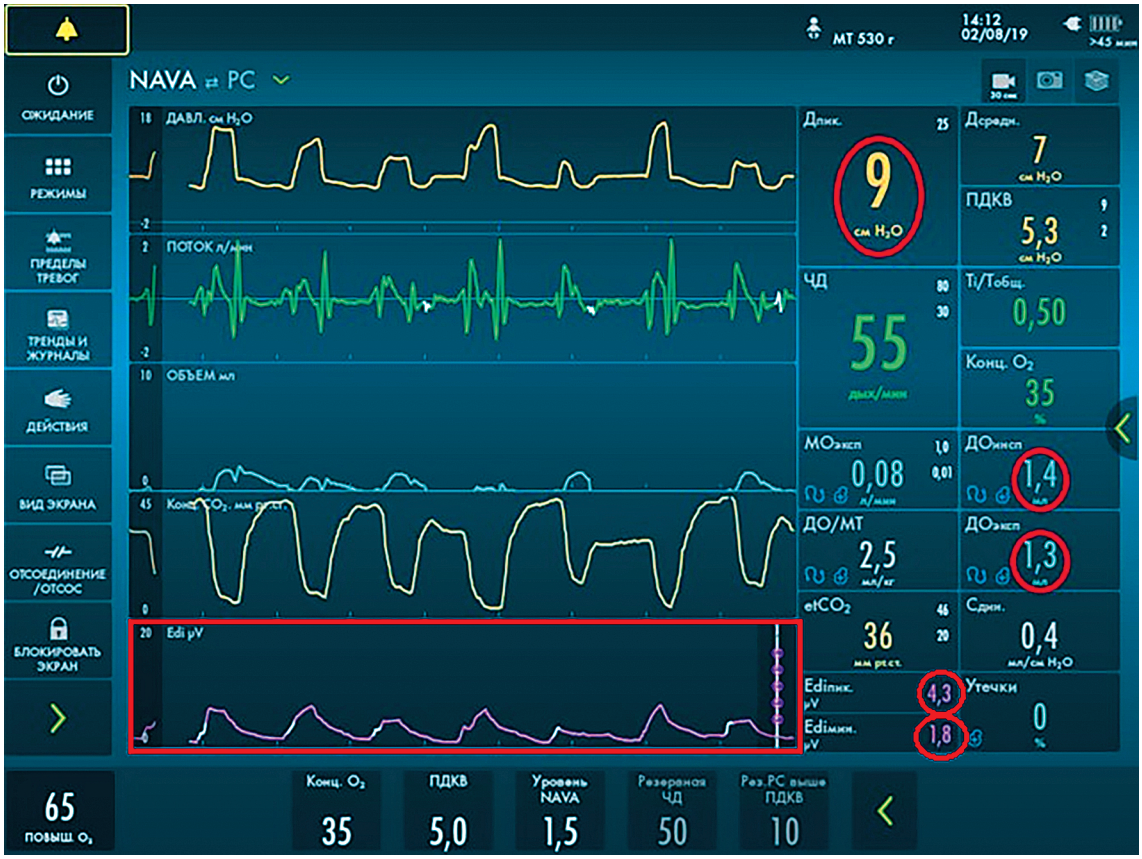

Fig. 3. Graphical monitoring of electrical activity of the diaphragm

Рис. 3. Графический мониторинг электрической активности диафрагмы

focal echocardiography, neurosonography, laboratory and bacteriologic screening were performed.

RESULTS

According to the chest radiography performed on admission, the was a radiographic picture of severe respiratory distress syndrome, pronounced decrease in left lung airiness (Fig. 1).

However, taking into account effective spontaneous breathing and stable saturation level of more than 95%, the child was transferred to noninvasive NAVA. After 6 hours, a review radiography of the chest was repeatedly performed. There was a distinct positive dynamics in the form of restoration of airiness of both lungs (Fig. 2).

According to the results of focal echocardiography performed on the first day of life, there was an increase in the volume blood flow in the pulmonary artery and the presence of an open ductus arteriosus with cerebral blood flow disturbance of hypoperfusion type.

On the second day of life, a moderate increase in the volume blood flow in the pulmonary artery remained, the arterial duct remained open, but there was restoration of blood flow in the cerebral vessels. On the third day of life, the volume blood flow in the pulmonary artery normalized, the arterial duct decreased more than 2 times, cerebral and mesenteric blood flows were not disturbed. On the fourth day the arterial duct spontaneously closed. Myocardial contractility was not disturbed, afterload corresponded to the age norm (Table 1).

No pathologic changes were observed in the blood gas composition during the first three days, and pH, pCO_2, pO_2, BE and lactate indices corresponded to the reference values (Table 2).

Graphical analysis of diaphragm electrical activity reflected good neuromuscular interaction and efficient operation of the respiratory musculature. The median values of maximum diaphragm electrical activity were [5.6;18.8]cmHg/μV, indicating adequate respiratory support proportional to the child's needs (Fig. 3).

DISCUSSION

The clinical case is fully justified using non-invasive NAVA as a starting regimen of respiratory therapy. If spontaneous breathing is preserved, it does not only synchronize the machine breaths with the child's respiratory attempt, but also performs them in proportion to the child's needs by analyzing the strength of muscle contraction. This allows to avoid excessive ventilation, maintaining the constancy of the blood gas composition. According to the data of chest radiography, the recovery of lung airiness was noted in 6 hours, and the child did not require "toughening" of ventilation parameters. It is shown that this method of ventilation has no negative effect on systemic and cerebral hemodynamics. NAVA created the pressure that does not affect the contractility of myocardium and left ventricular afterload, thus does not interfere with restructuring of blood circulation in the first day of life.

Thus, the use of noninvasive NAVA as a starting method of respiratory support in profoundly premature neonates is not only possible, but also promising. Rapid recovery of pulmonary function, stabilization of systemic and cerebral hemodynamics are the result of effective ventilation as close as possible to physiological breathing.

CONCLUSION

Not so long ago, the possibility of preserving spontaneous breathing in a profoundly premature infant was out of the question. As a rule, resuscitation in the delivery room ended with tracheal intubation and transfer to forced ventilation. Now the use of intelligent modes of non-invasive ventilation allows to completely revise this tactic. Nowadays, the use of intelligent modes of non-invasive ventilation allows to completely revise this tactic and use those ventilation methods that preserve and maintain effective independent breathing of the child from the first minutes 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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

прочли и одобрили финальную версию перед публикацией.

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

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

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

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ISSN 2221-2582

UDC 616.5-006.25-091-053.2+618.11-006.2+616-072.1-089.8
DOI: 10.56871/CmN-W.2024.22.32.018

PELVIC EPIDERMOID CYST IN A TEENAGER: AN EXTREMELY RARE CLINICAL CASE

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For citation: Osipov IB, Krasil'nikov DE, Lebedev DA, Chepelev AS, Ignat'ev VV. Pelvic epidermoid cyst in a teenager: an extremely rare clinical case. Children's Medicine of the North-West. 2024;12(3):152–157. DOI: https://doi.org/10.56871/CmN-W.2024.22.32.018

Received: 13.06.2024 **Revised: 01.08.2024** **Accepted: 10.09.2024**

Abstract. Epidermoid cysts are defined as benign tumors of the skin that evaluate from the ectodermal germ layer. Typical localization is face, neck, scalp, hands, and much less frequently described unusual locations: brain, gonads, spleen, kidneys. The evolution of cysts of atypical localization is associated with impaired migration of ectoderm cells during embryogenesis. An epidermoid cyst in the child's pelvic is an extremely rare clinical case. In the available literature, only two descriptions of epidermal cysts of pelvic localization among children are found. The clinical course of epidermoid cysts can be asymptomatic or accompanied by pain, lower urinary tract symptoms, disruption of internal organs. Indications for surgical treatment of such cysts are their possible inflammation, compression of neighboring organs with disruption of their function, and an extremely low but probable risk of malignancy. We present a clinical case of successful minimally invasive treatment of a 17-year-old boy with a pelvic epidermoid cyst, suffering from long-term abdominal pain syndrome.

Keywords: *epidermal cyst, pelvic cyst, cysts in children, extraorgan cyst, pediatric urology, laparoscopy, surgical treatment*

ЭПИДЕРМАЛЬНАЯ КИСТА МАЛОГО ТАЗА У ПОДРОСТКА: ЭКСТРЕМАЛЬНО РЕДКИЙ КЛИНИЧЕСКИЙ СЛУЧАЙ

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Для цитирования: Осипов И.Б., Красильников Д.Е., Лебедев Д.А., Чепелев А.С., Игнатьев В.В. Эпидермальная киста малого таза у подростка: экстремально редкий клинический случай // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 152–157. DOI: https://doi.org/10.56871/CmN-W.2024.22.32.018

Поступила: 13.06.2024 **Одобрена: 01.08.2024** **Принята к печати: 10.09.2024**

Резюме. Эпидермальные кисты определяют как доброкачественные опухоли кожи, происходящие из эктодермального зародышевого листка. Типично они локализуются на лице, шее, волосистой части головы, кистях, значительно реже встречаются необычные локализации: головной мозг, гонады, селезенка, почки. Происхождение кист нетипичной локализации связано с нарушением миграции клеток эктодермы в процессе эмбриогенеза. Эпидермальная киста полости малого таза у ребенка — экстремально редкий клинический случай. В доступной литературе нами найдено всего два описания эпидермальных кист тазовой локализации у детей. Клиническое течение эпидермальных кист может быть как бессимптомным, так и сопровождаться болевым синдромом, нарушением мочеиспускания, нарушениями работы внутренних органов. Показаниями к хирургическому лечению таких кист являются их возможное воспаление,

сдавление соседних органов с нарушением функции и крайне низкий, но вероятный риск малигнизации. Нами представлен клинический случай успешного малоинвазивного лечения мальчика 17 лет с эпидермальной кистой малого таза, страдающего длительным абдоминальным болевым синдромом.

Ключевые слова: *эпидермальная киста, киста малого таза, кисты у детей, внеорганная киста, детская урология, лапароскопия, хирургическое лечение*

INTRODUCTION

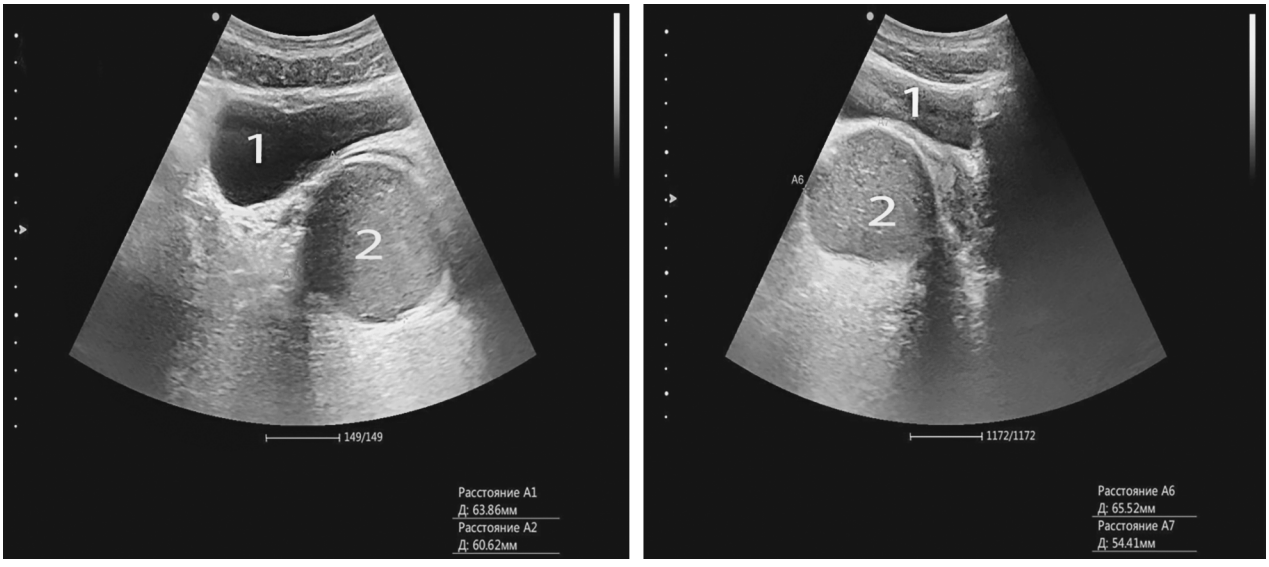
Epidermoid cysts (epidermal inclusion cysts) are defined as benign skin tumors developing from the ectodermal germinal sheet [1]. Most commonly, this pathology develops in individuals aged 19–45 years and usually the cysts are located on the face, scalp, neck, hand, and foot [1–3]. Unusual localizations such as brain, gonads, bones, spleen, kidney and other internal organs are much less common [4]. Usually, cysts do not bother patients and are discovered incidentally, but when they are large, they may compress neighboring organs, lead to lower urinary tract obstruction, pain syndrome or cause discomfort to patients [2, 4, 5]. The available literature describes two cases of treatment of children with pelvic epidermoid cysts. Thus, this type of localization is extremely rare in paediatric practice [3, 6].

CLINICAL CASE

Patient E., 17 years old, was admitted to the department of paediatric urology of St. Petersburg State Paediatric Medical University on 23 January 2023 with complaints of recurrent abdominal pain. According to the anamnesis: during the last year he was examined in a hospital at the place of residence due to painful abdominal syndrome, further ultrasound examination (USG) revealed a voluminous cystic formation in the small pelvis. After discharge he was consulted by a paediatric urologist-andrologist and sent for additional examination to the clinic of the Pediatric University.

Ultrasound: a rounded formation with thin walls was detected in the small pelvis, the formation was deforming the bladder, the content was of medium echogenicity, inhomogeneous, with hyperechogenic inclusions (Fig. 1).

Uroflowmetry: the curve is flattened, micturition volume — 400 ml, maximum flow rate — 17.4 ml/s, average flow rate — 7.8 ml/s, residual volume — 8 ml. Magnetic resonance imaging (MRI): the formation is located in the pelvis, up to 6.5 cm in size, to the left of the prostate gland, partially deforms the left lobe of the prostate, the content is fluid with inclusions (Fig. 2).



А/A Б/B

Fig. 1. Pelvis ultrasound: A — in the frontal plane; B — in the sagittal plane. 1 — bladder; 2 — epidermoid cyst

Рис. 1. УЗИ малого таза: А — во фронтальной плоскости; Б — в сагиттальной плоскости. 1 — мочевой пузырь; 2 — эпидермальная киста

Blood test: alpha-fetoprotein — 1.22 IU/ml (norm: 0.00–15.00 IU/ml), LDH — 157 units/L (norm: 125.00–220.00 units/l), beta-HCG — 1.3 IU/ml. The child was consulted by a paediatric oncologist — removal of the cystic neoplasm was recommended.

Intraoperative cystourethroscopy was performed to exclude the connection of the lower urinary tract with the cyst cavity, during which no signs of communication were detected. The bladder wall showed no visible changes. Laparoscopic trocars (5 mm) were placed in the periapical, left and right iliac regions. The peritoneum was dissected in the bladder apex, after which a tumor-like formation was identified and mobilized in the retrovesical space. The cyst was completely isolated and dissected, after which it was evacuated from the abdominal cavity. Doughy, granular, cream-colored contents were extracted at autopsy (Fig. 3, A).

The postoperative period was uncomplicated. The patient received antibacterial, symptomatic, and external therapy. The urethral catheter was removed on the 3rd day. Control uroflowmetry was performed on the 7th day after the operation. It showed an increase in the average flow rate from 7.8 ml/s to 9.3 ml/s, maximum flow rate from 17.4 ml/s to 20.7 ml/s with a micturition volume of 410 ml.

Tissue diagnostics: the cyst wall consists of fibrous connective tissue, with numerous dilated blood vessels, small focal hemorrhages. The cyst lining was formed by multilayer squamous keratinizing epithelium, which corresponds to the pathological picture of an epidermal cyst (Fig. 3, B). On the 7th day after surgery, the child was discharged.

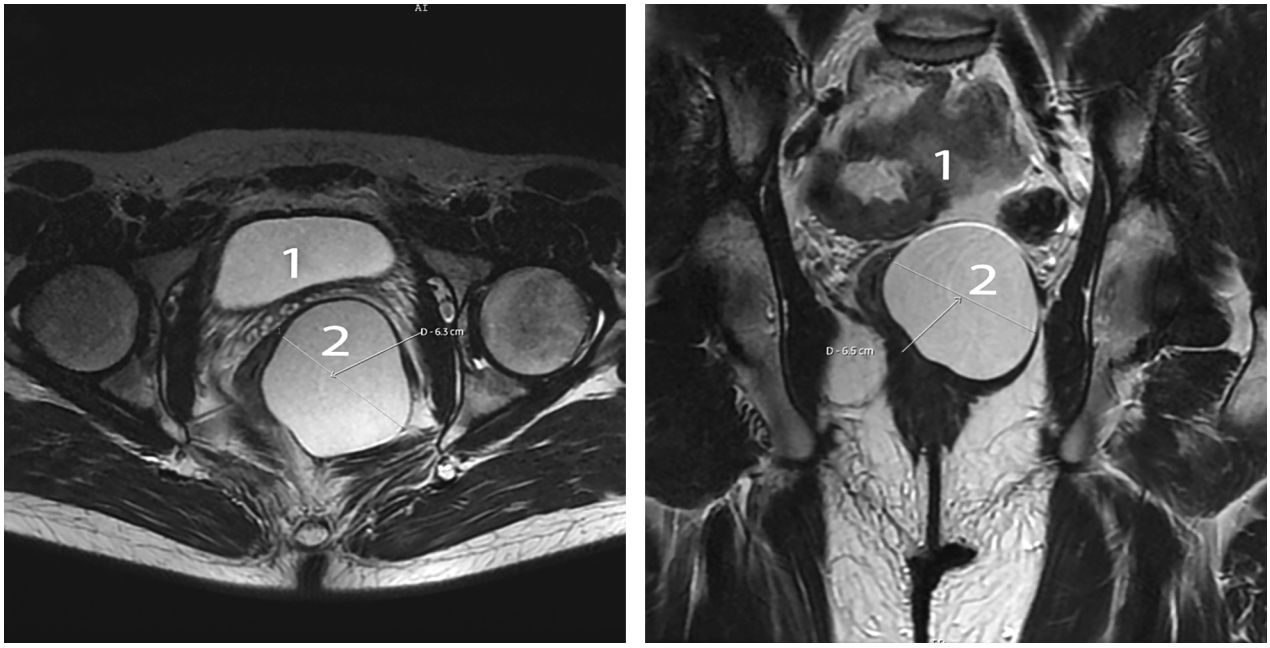
Next time, the boy was examined in the department after 1 year. There were no complaints of abdominal pain during this period, the patient feels healthy. There are no signs of new cystic formations in the pelvic cavity at ultrasound. Uroflowmetry curve was slightly flattened, average flow was 9.9 ml/s, maximum flow was 18.5 ml/s with a volume of 250 ml.

DISCUSSION

Epidermoid cysts are benign tumors of ectodermal origin. This pathology was first described by M.B. Dockerty and J.T. Pristley (1942) and defined as a cystic formation of unclear etiology [7].

A number of authors believe that the origin of congenital epidermal cysts is associated with embryonic implantation of ectoderm cells [2, 4, 5]. B. Fakhir et al. (2009) reported that acquired epidermal cysts can occur due to trauma or undergone surgery [5].

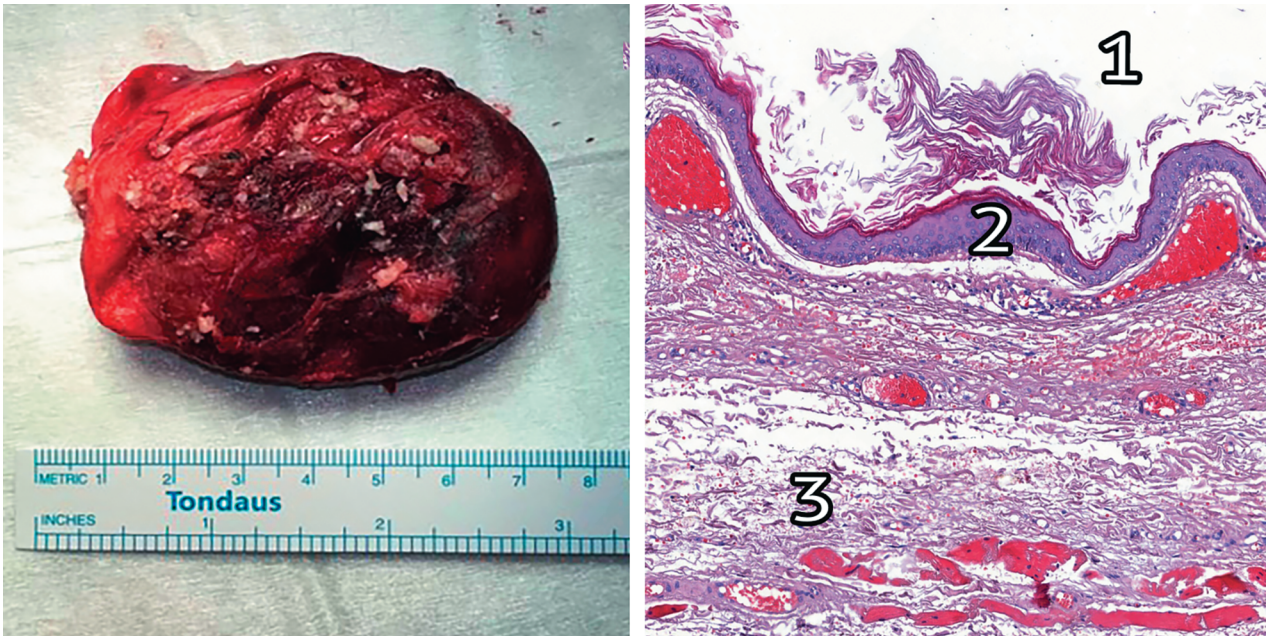
The typical localization for this pathology is the face, scalp, neck, chest and genital skin (scrotum,



a/*a* *б*/*b*

Fig. 2. MRI: *a* — frontal plane; *b* — sagittal plane. 1 — bladder; 2 — epidermoid cyst

Рис. 2. МРТ: *а* — фронтальная плоскость; *б* — сагиттальная плоскость. 1 — мочевой пузырь; 2 — эпидермальная киста



a/*a* *б*/*b*

Fig. 3. Removed cyst (*a*); histological specimen (*b*). 1 — cyst cavity; 2 — epithelial lining; 3 — fibrous connective tissue

Рис. 3. Удаленная киста (*а*); гистологический препарат (*б*). 1 — полость кисты; 2 — эпителиальная выстилка; 3 — волокнистая соединительная ткань

penis) [1, 2]. Unusual localizations such as the brain, gonads, bones, spleen, kidneys and other internal organs are described much less frequently [2, 3, 7, 8].

Epidermoid cyst located in the pelvis, which is not associated with internal organs, is an extremely rare clinical case. We found two descriptions of pelvic epidermoid cyst in a child in the available literature [3, 6]. Meanwhile, F.Z. Fdili Alaou et al. (2012) reported 15 cases of epidermoid cysts in adults [4].

N.S. Hyseni et al. (2009) believe that clinical manifestations depend on the compressive effect on organs and tissues. The patient described in their work suffered from abdominal bloating and pain [3]. In the second case presented by Y. Kato et al. (1998), the pathology was asymptomatic [6]. A number of authors also describe the development of pain syndrome, urinary disturbance due to urethral compression in adults [2, 5, 9]. In our clinical case, the patient was bothered by recurrent abdominal pain.

Large cysts can be palpated through the anterior abdominal wall, and sometimes the cyst can be palpated rectally [10]. In our clinical case, the cyst was not detected rectally.

Since epidermoid cysts are usually benign tumors, specific markers of malignant growth are informative only in cases of neoplastic transformation [2].

According to J. Pritesh et al. Pritesh et al. (2018), it is possible to visualize a delimited rounded formation of mixed echogenicity in ultrasonography [2]. F.Z. Fdili Alaoui et al. (2012) report that such formations in women can be taken for ovarian cysts [4].

According to a number of authors, computed tomography (CT) scans show the absence of a homogeneous fluid component in these cysts, which distinguishes them from other common cystic formations such as lipomas, fibromas, and desmoid tumors [2, 5, 8]. For a more accurate diagnosis, it is better to use MRI, in which it is possible to see a clearly delineated formation with a heterogeneous signal intensity in both T1- and T2-modes [4, 5, 10]. According to B. Fakhir et al. (2009), contrast accumulation by the surrounding tissues will allow to assess the nature of the cystic formation, as well as to predict the possibility and degree of mass effect [5].

According to most authors, histological examination demonstrates that an epidermal cyst is a cavity with fibrous connective tissue walls containing full-blooded vessels. The cyst lining consists of multilayered squamous keratinizing epithelium, and horny scales may be detected

in the lumen [2, 4, 10]. Our sample demonstrates the same histological picture.

The important differential sign distinguishing epidermal cysts from other cysts is the absence of skin appendages (sebaceous and sweat glands, hair follicles) [1]. Tumor diagnostics of the removed cyst showed no skin appendages in the cyst lumen.

Malignisation of such formations is considered improbable [1, 2, 4]. M.V. Kuritsyn (2006) describes 4 cases of malignant neoplasms formed from the epithelial lining of epidermoid cysts in 50–58-year-old women [11]. It is known that the proportion of children with neoplasms of various localizations can reach 2.3% [12] and that the main problem of paediatric oncology remains late diagnosis [13].

Oncological vigilance is one of the main directions of the diagnostic process against the background of increasing cancer morbidity rates in St. Petersburg, which is associated, among other things, with improving the quality of examination and increasing the vigilance of physicians with regard to cancer [14].

CONCLUSION

Pelvic epidermoid cyst in a child can manifest with prolonged abdominal pain syndrome. Surgical removal of the formation with subsequent histological examination is the only method of definitive diagnosis and treatment of this extremely rare pathology.

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ISSN 2221-2582

UDC 616.34-008.15-053.31-07-089
DOI: 10.56871/CmN-W.2024.52.77.019

CLINICAL CASE OF LEDD'S SYNDROME IN ADOLESCENCE

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For citation: Subbotin IV, Kholostova VV, Smirnov AN, Al-Mashat NA, Yarustovskiy PM, Dehkonboev AA, Akhmadjonov AM, Sytkov VV, Khavkin AI. Clinical case of Ledd's syndrome in adolescence. Children's Medicine of the North-West. 2024;12(3):158–162. DOI: https://doi.org/10.56871/CmN-W.2024.52.77.019

Received: 03.06.2024 **Revised: 09.07.2024** **Accepted: 10.09.2024**

Abstract. Ledd's syndrome is a common cause of intestinal obstruction in newborns, and in 90% of cases — in children under 1 year. At the same time, diagnostics and surgical treatment in this age period are not difficult. The authors analyzed 15-year experience of treating 51 children of older age groups with Ledd's syndrome and showed that its course in adolescence often has a nonspecific clinical picture, as well as an asymptomatic course, which can cause such conditions as hypotrophy, malabsorption syndrome, constipation, gastroesophageal and duodenogastric reflux and gastroduodenitis. The article presents the experience of treating a child with Ledd's syndrome in adolescence, demonstrating the complexity of diagnosis and treatment of older children.

Keywords: *Ledd's syndrome, Ledd's syndrome in adolescents and adults, diagnostics, surgical treatment*

КЛИНИЧЕСКИЙ СЛУЧАЙ СИНДРОМА ЛЕДДА В ПОДРОСТКОВОМ ВОЗРАСТЕ

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Для цитирования: Субботин И.В., Холостова В.В., Смирнов А.Н., Аль-Машат Н.А., Ярустовский П.М., Дехконбоев А.А., Ахмаджонов А.М., Сытьков В.В., Хавкин А.И. Клинический случай синдрома Ледда в подростковом возрасте // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 158–162. DOI: https://doi.org/10.56871/CmN-W.2024.52.77.019

Поступила: 03.06.2024 **Одобрена: 09.07.2024** **Принята к печати: 10.09.2024**

Резюме. Синдром Ледда — нередкая причина кишечной непроходимости у новорожденных, и в 90% случаев — у детей до 1 года. При этом диагностика и хирургическое лечение в этом возрастном периоде не представляет сложностей. Авторами проанализирован 15-летний опыт лечения 51 ребенка старших возрастных грууп с синдромом Ледда и показано, что его течение в подростковом периоде часто имеет неспецифическую клиническую картину, а также бессимптомное течение, что может явиться причиной таких состояний, как гипотрофия, синдром мальабсорбции, запоры, желудочно-пищеводный и дуодено-гастральный рефлюкс и гастродуоденит. В статье представлен опыт лечения ребенка с синдромом Ледда в подростковом периоде, демонстрирующий сложность диагностики и лечения детей старшей возрастной группы.

Ключевые слова*: синдром Ледда, синдром Ледда у подростков и взрослых, диагностика, хирургическое лечение*

INTRODUCTION

Ledd's syndrome (LS) is an uncommon cause of intestinal obstruction in neonates, with a incidence of 0.8:1000 [1, 2]. About 90% of cases of Ledd's syndrome manifest prior to 1 year of age. K. Fang et al. indicate that only 10% of cases of Ledd's syndrome are detected after the first year of life [3, 4]. The incidence of Ledd's syndrome in adult patients ranges from 0.0001 to 0.2%, and about 15% of such people do not have any clinical manifestations for a long period of life [5, 6].

Diagnosis and surgical treatment of Ledd's syndrome as a cause of intestinal obstruction in neonates is not difficult. However, the prolonged asymptomatic course of LS in children and adolescents lead to late diagnosis, and further formation of acute and chronic pathological conditions that threaten the child's life. In this regard, children with LS are often repeatedly hospitalized in various departments (more often — in gastroenterological ones), receive symptomatic treatment and are discharged in a state of compensation without receiving etiotropic treatment. As an intraoperative finding in a number of cases, Ledd's syndrome causes significant difficulties in adopting the correct surgical tactics during surgery [7].

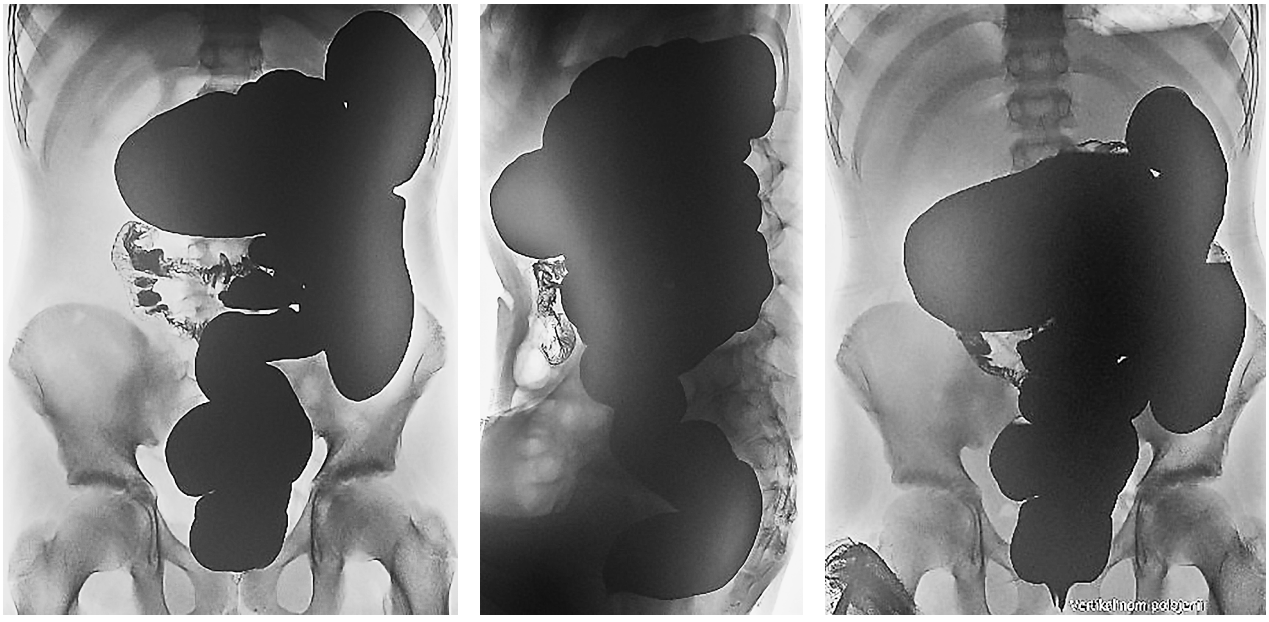
CLINICAL CASE

The clinical case presented in this article demonstrates the complexity of diagnosis and treatment of adolescents with LS.

Patient E., 14 years old, male, came to the clinic with complaints of abdominal pain, irregular stools, nausea and vomiting. It is known from the anamnesis that the child has been having nausea and vomiting periodically since birth. Recently, abdominal pain, constant vomiting, weight loss has been noted. The child has repeatedly received inpatient treatment at the place of residence, as well as in the department of gastroenterology, but with no positive results. He was hospitalized in the surgical department of the clinic. Objective examination showed hypotrophy of the I degree. General condition is satisfactory, in consciousness. The skin is dry, pale pink, without rashes. Subcutaneous fatty tissue is moderately developed, skin turgor and elasticity are preserved. There are no visible swellings on the face. Breathing through the nose, free. The chest participates in the act of breathing, symmetrical. Vesicular breathing is heard above the lungs. Tones are clear, pulse is rhythmic. The mucous membrane of the oral cavity is clean, pale pink, the tongue is moist, without rashes. The abdomen is oval, symmetrical, not bloated, participates in the act of breathing. During the palpation the abdomen is soft, painful around the umbilicus. There is no dulling in flanks. Stools are irregular.

The perianal area is featureless. Tone of anal sphincter is not changed. The ampulla of the rectum is filled with fecal mass of hard consistency. There were no significant changes in clinical and biochemical blood and urine analysis parameters. According to the results of ultrasonography (USG), no signs of gallbladder deformation were revealed. According to esophagogastroduodenofibroscopy (EFGDS) there is insufficiency of esophageal cardia of the I degree. Reflux esophagitis of the I degree. Diffuse gastroduodenitis with hyperaemia of the mucosa. Enlargement of the duodenum. Multislice computed tomography-angiography was also performed, which revealed signs of narrowing of the aortomesenteric angle — compression of the left renal vein between the aorta and the superior mesenteric artery cannot be excluded. Partial small bowel obstruction — an abnormality of bowel rotation and fixation cannot be excluded. The angle of superior mesenteric artery branching is 9°.

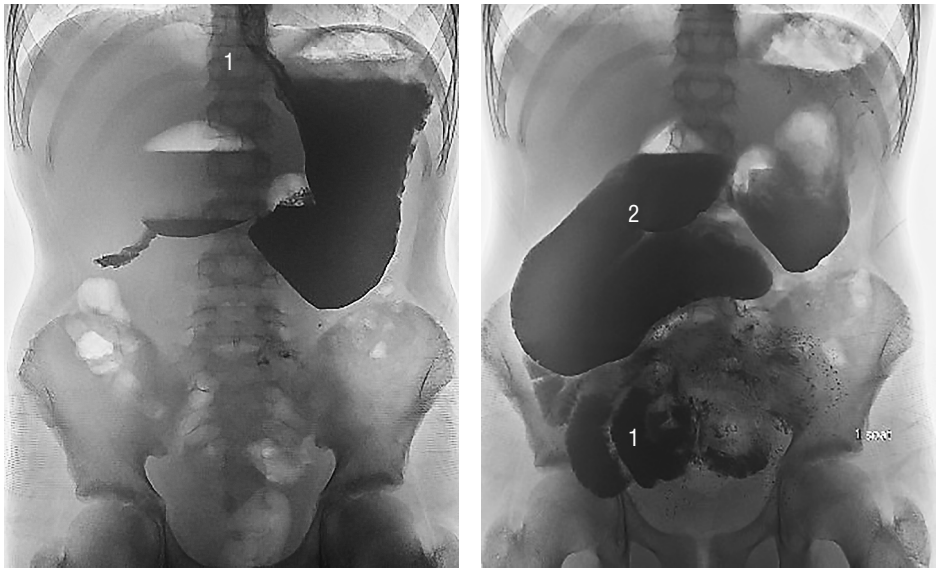
 ISSN 2221-2582



а/a *б/b* *в/c*

Fig. 1. Irrigography. High location (*a*) of the dome of the cecum, median (*b*) and left-sided (*c*) location of all parts of the large intestine

Рис. 1. Ирригография. Высокое расположение (*а*) купола слепой кишки, срединное (*б*) и левостороннее (*в*) расположение всех отделов толстой кишки



а *б*

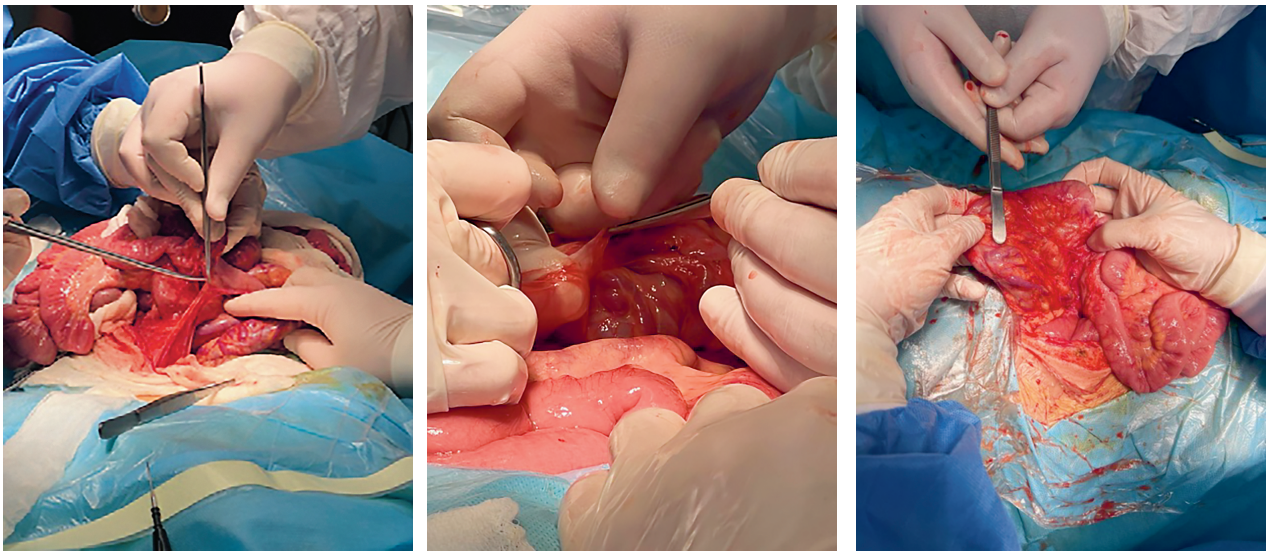
Fig. 2. X-ray contrast study of the upper gastrointestinal tract with barium sulfate (*a*: 1 —gastroesophageal reflux; *b*: 1 — symptom of "spring"; 2 — megaduodenum)

Рис. 2. Рентгеноконтрастное исследование верхних отделов желудочно-кишечного тракта с сульфатом бария (*а*: 1 — желудочно-пищеводный рефлюкс; *б*: 1 — симптом «пружины»; 2 — мегадуоденум)

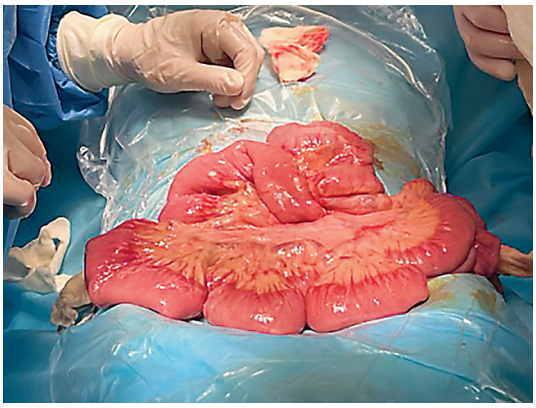
Irrigography revealed a high location of the cecal dome, predominantly on the left side and medial location of all parts of the colon (Fig. 1).

X-ray contrast study of the upper gastrointestinal tract revealed gastresophageal reflux (Fig. 2, *a*), megaduodenum (Fig. 2, *b*), "spring" symptom (Fig. 2, *b*), reflecting the spiral course of the initial parts of the small intestine, predominantly right-sided location of the small intestine (Fig. 2).

A laparotomy was performed, which revealed Ledd's tracts, small intestine fasciculation, and significantly dilated mesenteric vessels (Fig. 3, *b*). The congenital fetal adhesions were



а/a *б/b* *в/c*



г/d

Fig. 3. Separation of the strands of Ledd (*a*); significant expansion of the mesenteric vessels (*b*, *c*), intraoperative picture after straightening the mesentery (*d*)

Рис. 3. Разделение тяжей Ледда *(а)*; значительное расширение сосудов брыжейки *(б, в)*; интраоперационная картина после расправления брыжейки *(г)*

separated (Fig. 3, *a*), detorsion and spreading of the pericardium were performed. Intestinal passage was restored on the 3rd day. The child was discharged home on the 7th day.

Over a fifteen-year period we have accumulated experience in treating 51 children with Ledd's syndrome. Obviously, the course of LS in adolescence often has a nonspecific clinical picture, as well as asymptomatic course, which, due to its rare occurrence in children and adolescents, is the cause of pathological conditions of gastroenterological profile (such as hypotrophy, malabsorption syndrome, constipation, gastresophageal and duodenogastric reflux, gastroduodenitis, bulbitis). Children with a gastroenterological complaints, episodes of vomiting with light intervals should undergo a comprehensive examination, including X-ray contrast examination, fibrogastroduodenoscopy, expert ultrasound scanning, and, if a characteristic clinical picture is detected, laparotomy with separation of Ledd's ligaments, detorsion of the ductus and mesenteric spreading should be performed.

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

ISSN 2221-2582

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

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

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

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UDC 616.348-007.61-053.2-07-089.844+616.714.1-007.125-08-06-084
DOI: 10.56871/CmN-W.2024.27.68.020

FEATURES OF THE COURSE OF HIRSCHSPRUNG'S DISEASE IN PATIENTS WITH DOWN SYNDROME AND OTHER GENETIC ANOMALIES

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For citation: Akhmadjonov AM, Dehkonboev AA, Aliev MM, Kholostova VV, Smirnov AN, Al-Mashat NA, Yarustovskiy PM, Sytkov VV, Khavkin AI. Features of the course of Hirschsprung's disease in patients with Down syndrome and other genetic anomalies. Children's Medicine of the North-West. 2024;12(3):163–172. DOI: https://doi.org/10.56871/CmN-W.2024.27.68.020

Received: 14.06.2024 **Revised: 12.07.2024** **Accepted: 10.09.2024**

Abstract. *Introduction.* The incidence of Hirschsprung's disease (HD) in patients with Down syndrome (DS) is significantly higher than in the population and ranges from 2.76 to 16%. The article examines the features of the course of the disease in patients with HD and DS, risk factors for complications and ways to prevent and treat them. *Objective*. The objective of the presented work was to analyze the prevalence of Hirschsprung's disease in children with Down syndrome, as well as to identify risk factors for the development of complications, and to develop strategies for the prevention and treatment of this group of patients.*Materials and methods.* During the period from 2016 to 2024, 14 children (3.8%) with concomitant genetic diseases were operated on at the Filatov Children's Hospital for Pediatric Surgery: Down syndrome — 10 (2.7%), Moyatt–Wilson — 2 (0.54%), Sturge–Weber — 1 (0.27%) and ondine syndrome — 1 (0.27%). The average age was 1.8 years (from 1 month to 6 years). The total form was diagnosed in 2 cases (14.2%), subtotal — in 2 (14.2%), in other children — recto-sigmoid form (71.6%). Three children (21.4%) had a stoma — ileostomy previously applied to two children with extended agangliosis (14.2%) and a sigmostomy to the 1 child. *Results.* The majority of children had early (7–50%) or late (3–21.4%) complications: 4 children had a failure of the colorectal anastomosis (CRA). The treatment outcomes were as follows: permanent stoma in 2 (14.2%) children, fecal incontinence in 5 patients (35.7%), rectal stenosis developed in 2 cases (14.2%). One child died on the background of persistent peritonitis with concomitant primary immunodeficiency syndrome (7.1%). A favorable long-term result was achieved in 6 cases (42.8%). *Conclusions.* Given the higher risk of developing CRA failure in patients with HD+DS, preventive stomas or 2-stage interventions should be more widely used, which can significantly reduce the risk of inflammatory complications in the postoperative period.

Keywords: *Hirschsprung's disease, Down syndrome, prevention of complications, treatment tactics*

ОСОБЕННОСТИ ТЕЧЕНИЯ БОЛЕЗНИ ГИРШПРУНГА У ПАЦИЕНТОВ С СИНДРОМОМ ДАУНА И ДРУГИМИ ГЕНЕТИЧЕСКИМИ АНОМАЛИЯМИ

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ISSN 2221-2582

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Для цитирования: Ахмаджонов А.М., Дехконбоев А.А., Алиев М.М., Холостова В.В., Смирнов А.Н., Аль-Машат Н.А., Ярустовский П.М., Сытьков В.В., Хавкин А.И. Особенности течения болезни Гиршпрунга у пациентов с синдромом Дауна и другими генетическими аномалиями // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 163–172. DOI: https://doi.org/10.56871/CmN-W.2024.27.68.020

Поступила: 14.06.2024 **Одобрена: 12.07.2024** **Принята к печати: 10.09.2024**

Резюме. *Введение.* Частота болезни Гиршпрунга (БГ) у пациентов с синдромом Дауна (СД) значительно выше, чем в популяции, и составляет от 2,76 до 16%. В статье рассматриваются особенности течения заболевания у пациентов с БГ в сочетании с СД, факторы риска развития осложнений и пути их профилактики и лечения. *Цель* представленной работы заключалась в анализе распространенности болезни Гиршпрунга у детей с синдромом Дауна, а также выявлении факторов риска развития осложнений, выработке стратегий профилактики и лечения данной группы пациентов. *Материалы и методы.* За период с 2016 по 2024 г. в клинике детской хирургии ДГКБ им. Н.Ф. Филатова оперированы 14 детей (3,8%) с сопутствующими генетическими заболеваниями: синдромом Дауна — 10 (2,7%), Моятт–Вильсона — 2 (0,54%), Стурге–Вебера — 1 (0,27%) и синдром «ундины» — 1 (0,27%). Средний возраст составил 1,8 года (от 1 месяца до 6 лет). Тотальная форма диагностирована в двух случаях (14,2%), субтотальная — в двух (14,2%), у остальных детей — ректосигмоидная форма (71,6%). Трем детям (21,4%) предварительно была наложена стома — илеостома двум детям с протяженным агангliозом (14,2%) и одному ребенку — сигмостома. *Результаты.* У большинства детей имели место ранние (7–50%) или поздние (3–21,4%) осложнения: у четырех детей наблюдалась несостоятельность колоректального анастомоза (КРА). Исходы лечения были следующими: постоянное стоманосительство — 2 (14,2%) ребенка, недержание кала — у 5 пациентов (35,7%), стеноз прямой кишки развился в 2 случаях (14,2%). Один ребенок погиб на фоне некупирующегося перитонита при сопутствующем синдроме первичного иммунодефицита (7,1%). Благоприятный отдаленный результат удалось достичь в 6 случаях (42,8%). *Выводы.* Учитывая высокий риск развития несостоятельности колоректального анастомоза (КРА) у пациентов с СД+БГ, следует шире использовать превентивные стомы или двухэтапные вмешательства, что может существенно снизить риск воспалительных осложнений в послеоперационном периоде.

Ключевые слова: *болезнь Гиршпрунга, синдром Дауна, профилактика осложнений, тактика лечения*

INTRODUCTION

According to the literature, the incidence of Hirschsprung's disease (HD) in Down syndrome (DS) ranges from 2.76 to 16% (1.4), and the incidence of DS in patients with HD ranges from 1 to 9% (2.4), that is, the combination of HD+SD in the population is significantly higher than the overall incidence of HD. Numerous studies have proved that the severity of clinical manifestations and the frequency of various complications are higher in patients with DS. The article is devoted to the analysis of HD treatment in patients with DS and some other hereditary syndromes.

AIM

The aim of the study is to analyze the prevalence of Hirschprung's disease in children with Down syndrome, as well as to identify risk factors for the development of complications, to develop strategies for prevention and treatment of this group of patients.

MATERIALS AND METHODS

In the period from 2016 to 2024, 367 patients underwent laparoscopic assisted surgery for Hirschprung's disease by means of the Soave-

Georgeson technique. The surgeries took place in the paediatric surgery clinic of the N.F. Filatov Children's Hospital. All patients were older than the neonatal period. Among these patients, 14 children (3.8%) had concomitant genetic diseases: Down syndrome — 10 (2.7%), Moyatt–Wilson syndrome — 2 (0.54%), Sturge–Weber syndrome — 1 (0.27%) and 'Ondine's curse' syndrome — 1 (0.27%). Undoubtedly, these syndromes have fundamental differences, however, the majority of children had similar features of the postoperative period, thus, we decided to analyze the case histories of all the above-mentioned patients as well. The patients' data are summarized in Table 1.

TREATMENT RESULTS

Most of the children were male, only one girl had Down syndrome and another had Sturge–Weber syndrome. The HD was diagnosed at a median age of 1.8 years (1 month to 6 years), which is now considered relatively late, taking into account that alertness for HD should be high in this group of patients. The distribution by length of agangliosis did not differ compared to general population — the total form was diagnosed in two cases (14.2%), subtotal — in two cases (14.2%), the remaining children had the rectosigmoid form (71.6%).

Three children (21.4%) had a preliminary stoma applied: two children with extended agangliosis were iliostomized (14.2%) and one child was sigmostomized.

The overall complication rate in this group of patients was very high. Postoperative period proceeded without any peculiarities in three cases (21.4%), the rest of the children had early (7–50%) or late (3–21.4%) complications. Early postoperative complications were represented by cases of colorectal anastomosis (CRA) failure: four children had CRA failure of grade III-IV according to our classification (Figs. 1, 2) and were accompanied by pelvic (3–21.4%) and spilled (1–7.1%) peritonitis. One child had a 60 mm circular necrosis of the descended intestine, while the other had CRA failure with normal fixation of the descended intestine and necrosis of perineal soft tissues.

The most severe late complications included the development of paraproctitis and rectoperineal fistula in 1 year after surgery (Fig. 3), which required colostomy. Taking into account the severe degree of mental deficit and difficulties in care, the parents refused to close the stoma afterwards. The child is a permanent stoma carrier. A life-threatening complication in the form of severe Hirschprung-associated colitis of clostridial etiology developed 9 years after the initial operation. Hirschprung-associated enterocolitis (HAEC) had a severe course, complicated by fibrinous purulent peritonitis and multiorgan failure. The child was operated: lavage and drainage of the abdominal cavity and ileostomy were performed. On the background of treatment, including powerful antibacterial therapy, constant lavage of

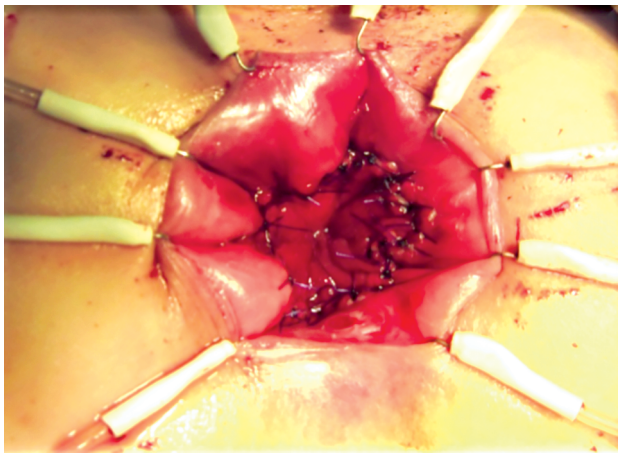

Fig. 1. Appearance of the colorectal anastomosis in child G., 6 years old, the reduced intestine is bright pink, the blood supply is beyond doubt

Рис. 1. Внешний вид колоректального анастомоза у ребенка Г., 6 лет, низведенная кишка ярко-розового цвета, кровоснабжение не вызывает сомнений

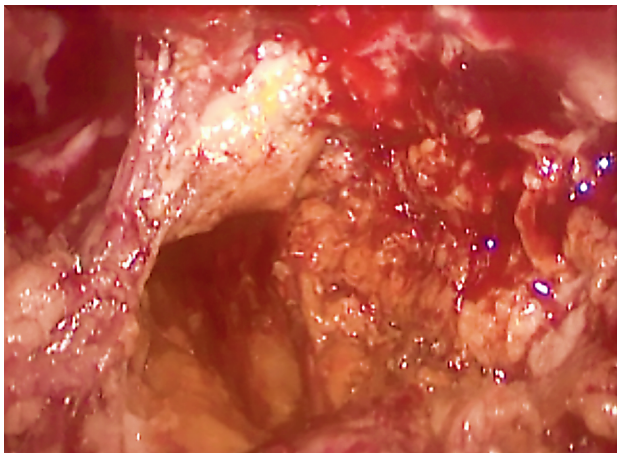

Fig. 2. Laparoscopic picture: 6 days after colon reduction in child G., 6 years old — retrorectal abscess, ischemic circular necrosis of the colon reduction, pelvic peritonitis

Рис. 2. Лапароскопическая картина: 6-е сутки после низведения толстой кишки у ребенка Г., 6 лет — ретроректальный абсцесс, ишемический циркулярный некроз низведенной кишки, тазовый перитонит

ISSN 2221-2582

Table 1. Characteristics of patients with Hirschsprung disease and associated genetic syndromes

Таблица 1. Характеристика пациентов с болезнью Гиршпрунга и сопутствующими генетическими синдромами

№ п/п	Пол ребенка и возраст на момент операции низведения / Gender of the child and age at the time of reduction surgery	Генетический синдром и сопутствующие врожденные пороки развития (ВПР) и заболевания / Genetic syndrome and associated congenital malformations (CMF) and diseases	Форма заболевания / Form of the disease	Предварительное стомирование / Pre- ostomy	Осложнения / Complications	Сроки развития осложнений с момента операции / Time frame for the development of complications from the moment of surgery	Стомирование на этапах коррекции осложнений / Ostomy at the stages of correction of complications	Исход / Exodus
1	Мальчик, 1 месяц / Boy, 1 month	С-м Моятт–Вильсона / Moyatt-Wilson S-m	Ректосигмоидная / Recto-sigmoid	–	Парапроктит, ректоперинеальный свищ / Rectoperineal fistula	1 год / 1 year	+	Постоянная стома / Permanent stoma
2	Мальчик, 3 месяца / Boy, 3 month	С-м Моятт–Вильсона / Moyatt-Wilson S-m	Ректосигмоидная / Recto-sigmoid	–	ГАЭК, псевдомембранозный колит, сепсис / GAEC, pseudomembranous colitis, sepsis	9 лет / 9 years	+	Благоприятный / Favorable
3	Девочка, 1 год / Girl, 1 year	С-м Стурге–Вебера / Sturge-Weber S-m	Ректосигмоидная / Recto-sigmoid	–	Стеноз КРА, ятрогенный разрыв НАС / CRA stenosis, iatrogenic rupture of the EAS	6 месяцев / 6 months	+	Реконструктивная операция на промежности, стеноз КРА, недержание кала / Reconstructive surgery of the perineum, cranial stenosis, fecal incontinence
4	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Recto-sigmoid	–	–	–	–	Благоприятный / Favorable
5	Мальчик, 3 месяца / Boy, 3 month	С-м Дауна (острый лейкоз) / S-m Down (acute leukemia)	Тотальная / Total	Илеостома / Ileostomy	Несостоятельность илеоилеоанастомоза, абсцесс брюшной полости, сепсис / Failure of ileo-ileoanastomosis , abdominal abscess, sepsis	1 месяц / 1 month	+	Недержание кала / Fecal incontinence
6	Мальчик, 6 лет / Boy, 6 years old	С-м Дауна / Down S-m	Ректосигмоидная / Recto-sigmoid	–	Циркулярный некроз низведенной кишки, тазовый перитонит / Circular necrosis of the reduced intestine, pelvic peritonitis	6-е сутки / 6th day	+	Стеноз КРА I степени Недержание кала II степени / 1st degree CRA stenosis Stage 2 fecal incontinence
7	Мальчик, 5 лет / Boy, 5 years old	С-м Дауна / Down S-m	Субтотальная / Subtotal	–	Несостоятельность КРА / Insolvency of the CRA	12-е сутки / 12th day	+	Постоянная стома / Permanent stoma

ISSN 2221-2582
Children's medicine of the North-West
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8	Девочка, 1 год / Girl, 1 year	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	Сигмостома / Sigmostoma	–	–	–	Благоприятный / Favorable
9	Мальчик, 8 месяцев / Boy, 8 months	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Некроз мягких тканей промежности / Necrosis of soft tissue of the perineum	8-е сутки / 8th day	+	Наложение вторичных швов. Ректальный пролапс. Недержание кала / Application of secondary sutures. Rectal prolapse. Fecal incontinence
10	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Несостоятельность КРА, разлитой каловый перитонит / CRA failure, diffuse fecal peritonit	6-е сутки / 6th day	+	Благоприятный / Favorable
11	Мальчик, 1 год / Boy, 1 year	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	–	–	–	Благоприятный / Favorable
12	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Несостоятельность КРА, тазовый перитонит / CRA failure, pelvic peritonitis	5-е сутки / 5th day	+	Благоприятный / Favorable
13	Мальчик, 11 месяцев / Boy, 11 months	С-м «ундины» / S-m “undines”	Субтотальная / Subtotal	Илеостома / Ileostomy	Стеноз КРА / CRA stenosis	1 месяц / 1 month	–	Недержание кала II степени / Stage 2 fecal incontinence
14	Мальчик, 9 месяцев / Boy, 9 months	С-м Дауна / Down S-m	Тотальная / Total	–	Деструктивный аппендицит, лизис аппендикса, заворот подвздошной кишки / Destructive appendicitis, appendix lysis, ileal volvulus	5-е сутки / 5th day	+	Разлитой перитонит на фоне первичного иммунодефицита, внутрибрюшные абсцессы. Летальный исход / Diffuse peritonitis against the background of primary immunodeficiency, intra-abdominal abscesses. Death

Note: CMA — congenital malformations; HAEC — Hirschsprung-associated enterocolitis; CRA — colorectal anastomosis; EAS — external anal sphincter.

***Примечание*:** ВПР — врожденные пороки развития; ГАЭК — Гиршпрунг-ассоциированный энтероколит; КРА — колоректальный анастомоз; НАС — наружный анальный сфинктер.

 ISSN 2221-2582

the colon with metronidazole, use of methods of extracorporeal detoxification, the condition was finally stabilized. A year after the colitis, the child was examined, biopsy of the lowered intestine was performed and its normal ganglionic structure was confirmed, and the ileostomy was closed with subsequent favorable outcome. It was not possible to convincingly prove the obstructive nature of GAEC, as the child had no history of constipation before the development of this complication. Interestingly, both children with this complication had Moyatt-Wilson syndrome. It was not possible to convincingly prove the obstructive nature of Hirschprung associated enterocolitis (HAEC), as the child had no history of constipation before the development of this complication. Interestingly, both children with this complication had Moyatt–Wilson syndrome.

In order to correct the complications, 10 children (71.4%) had to undergo stoma surgery. Two patients (14.2%) became permanent stoma carriers. One child had iatrogenic damage of the external anal sphincter (NAS), the patient underwent reconstructive intervention on the perineum: sphincter plasty was performed. One child underwent secondary suturing due to colorectal anastomosis (CRA) failure on the background of perineal soft tissue necrosis. In all other cases, no additional interventions on the rectum were performed, and no secondary sutures were placed.

Among the comorbidities that could affect the treatment outcomes were: acute leukaemia (1–7.1%), primary immunodeficiency (1–7.1%). It is interesting to note that both children with blood disorders had total HD. Only one child had overweight, it was a patient with advanced extended necrosis of the lower intestine.

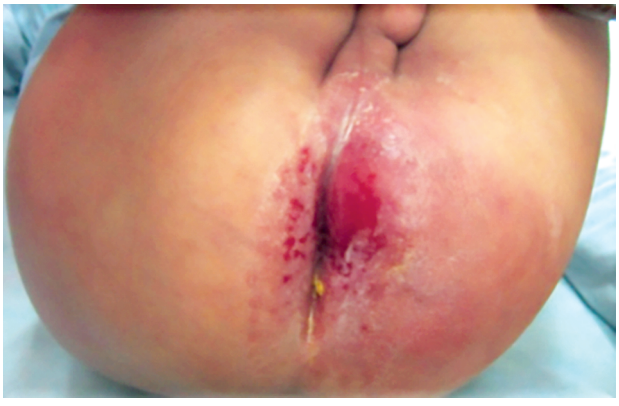


Fig. 3. Acute purulent paraproctitis in a patient after colon resection for Hirschsprung's disease

Рис. 3. Острый гнойный парапроктит у пациента после резекции толстой кишки по поводу болезни Гиршпрунга

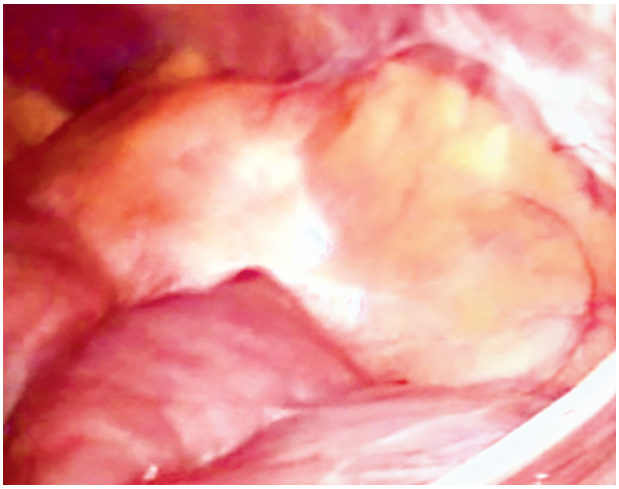
Anatomical peculiarities of the colon structure were revealed in three cases — retroperitoneal location of the left colon, scattered type of blood supply of the left colon, and excessive amount of adipose tissue making it difficult to verify angioarchitectonics in the mesentery of the sigmoid colon. It can be assumed that such anatomical prerequisites contributed to ischemic disorders in the descended colon (Fig. 4).

The outcomes of treatment were as follows: permanent stoma carrier — 2 (14.2%) children, fecal incontinence — 5 patients (35.7%), rectal stenosis developed in 2 cases (14.2%). One child died against the background of unrelieved peritonitis with concomitant primary immunodeficiency syndrome (7.1%). Favorable long-term outcome was achieved in 6 cases (42.8%).

DISCUSSION

The problem of treating surgical diseases in patients with various genetic syndromes is widely discussed in the literature, since these patients have peculiarities that affect the results of treatment at the stages of diagnosis, treatment and a postoperative period. Although there is due caution in the diagnosis of HD in DS patients, many authors indicate that the diagnosis is established later than in children without concomitant genetic syndromes. According to R.A. Saberi et al., during the neonatal period patients with DS are diagnosed with HD later ,(6th and 4th day after birth), and the duration of treatment is longer (22 and 15 days, respectively) [1, 2]. Due to the more severe course of the disease, up to 43% of patients with a combination of DS+HD require ostomy in the newborn period [4–6].

According to the summary data, the frequency of repeated operations in children with DM+BG ranges from 10 to 29% [7–9] due to the development of complications. Thus, according to A. Pini Prato et al., the probability of HAEC is 32% even before the surgery[4]. Similar data are published by D.R. Halleran et al. who analyzed the cases of HAEC on a large sample of patients, 14% of which were patients with DS. The severity of HAEC manifestations in these children was higher (7.1 and 5.6 points on the HAEC assessment scale), the frequency of tachycardia on admission was 75 and 19%, respectively, hypotension — 33 and 7%, the need for treatment in the intensive care unit — 58 and 12% [3]. Moreover,



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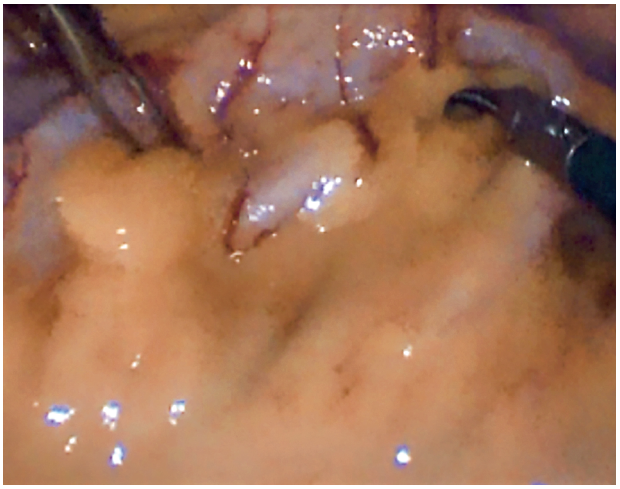

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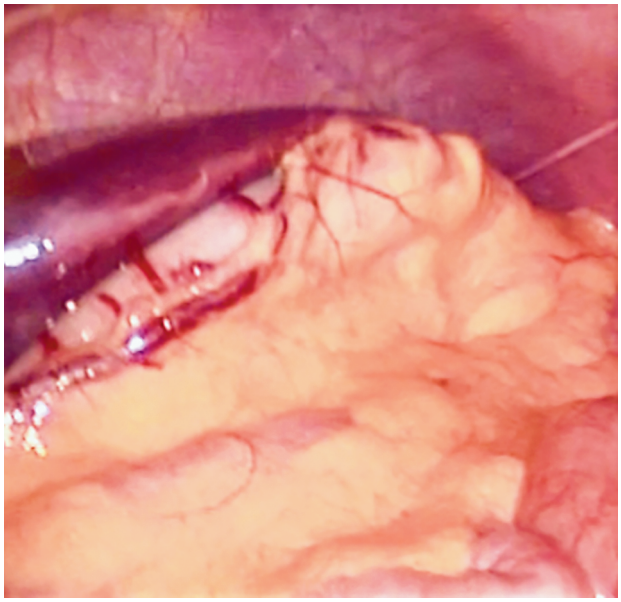

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Fig. 4. Laparoscopic picture of the abdominal cavity in a child with Down syndrome and Hirschsprung disease — an excessive amount of visceral fat around the colon: *a* — retroperitoneal location of the left parts of the colon, the intestine is in a "fat sheath"; *b* — an excessive amount of visceral fat in the sigmoid colon; *c* — fatty sheath around the transverse colon

Рис. 4. Лапароскопическая картина брюшной полости у ребенка с синдромом Дауна и болезнью Гиршпрунга — избыточное количество висцерального жира вокруг толстой кишки: *а* — забрюшинное расположение левых отделов толстой кишки, кишка в «жировом футляре»; *б* — избыточное количество висцерального жира в сигмовидной кишке; *в* — «жировой футляр» вокруг поперечного отдела ободочной кишки

the duration of illness before admission was almost 3 times longer (84 and 24 hours, respectively). The authors believe that this is due to the fact that children with mental deficits start complaining later. This may also explain the severity of manifestations. In addition, recent studies on the pathogenesis of HAEC show that susceptibility to HAEC in HD patients is partly due to impaired immune function of the intestinal mucosa, in particular impaired intestinal B-cell function and impaired IgA production [10, 11]. This dysfunction probably results in an inadequate respond to an infectious lesion, predisposing the patient to bacterial invasion and HAEC. Children with DS have a previously described predisposition to many infectious diseases and cancers. Moreover, specific studies have shown that patients with DS have an initial deficiency in both humoral and cellular immunity, resulting in profound B-lymphocytopenia and alterations in IgA production. However, a study by A.J.M. Dingemans et al. showed that the incidence of HAEC in HD patients does not depend on concomitant DS [10].

In addition to HAEC, numerous publications indicate a higher risk of surgical complications, according to R.A. Saberi et al. children with DS have a higher incidence of wound complications (12 and 3%) compared to patients without DS and ulcerative necrotizing enterocolitis (UNEEC) (14 and 5%) [2].

Patients with DM have a high risk of mortality. Thus, R.A. Saberi et al. reported that the mortality rate for HD in the newborn period is more than 4 times higher in children with DS (5 and 0.8%) [2]. In 2013, these rates were significantly higher — 12 and 4.2–5.5%, respectively [5]. These data are

ISSN 2221-2582

confirmed by studies of the Japanese Association of Paediatric Surgery conducted in 2009, according to which preoperative mortality of children with DS+HD decreased from 10 to 3%, and overall mortality decreased from 26 to 8% [6]. However, despite the positive trends, the mortality rate is still very high, as the overall mortality rate in HD does not exceed 1% according to the American Association for Paediatric Surgery [9–11].

Possible explanations include: less precise control of body dynamics and greater difficulty in maintaining balance when walking, which may be the result of documented cerebellar deficits, muscle hypotonia and ligament laxity in people with DS; co-activation of agonist-antagonist muscle groups; mitochondrial dysfunction and very low aerobic fitness. The oxygen uptake efficiency index, which determines an individual's exercise capacity, is lower in these patients, inevitably leading to poor adaptation to exercise. Arterial resistance in response to maximal exercise is reduced in people with DS.

Three cases revealed peculiarities of the anatomical structure of the left colon, which determine specific features of its blood supply and contribute to ischemia of the descending colon. No discussions of the issue were found in the literature. However, taking into account that patients with DS are more often overweight, the literature focuses on the influence of obesity and the development of complications after surgical interventions in these patients. Patients with DS have a specific constitutional type characterized not only by an overall excess of adipose tissue but also by an increased amount of visceral fat, a phenomenon observed even in malnourished children. Visceral fat is concentrated in the mesentery of the intestine, often with a scattered type of blood supply to the intestine, which directly affects the peculiarities of the blood supply to the descending colon. Overweight and obesity in DS are caused by slow metabolism, abnormal leptin concentration in blood and low level of physical activity. Patients with DS appeared to have significantly higher leptin levels than their siblings, and this is more pronounced than the body fat percentage would suggest. This may explain the increased risk of obesity. Leptin levels are higher in children with DS than in children without DS but with the same body mass index (BMI), whether or not obesity is present. This fact demonstrates leptin resistance in DS.

The tendency to apnea in patients with Down syndrome may play a role, as sleep apnea may precede obesity. Thus, A. Ravel et al. reported that 62% of obese children had a higher prevalence of large lingual tonsils and more often underwent palatine tonsillectomy [1].

The high incidence of inflammatory complications is probably due to the higher frequency of immunological abnormalities in children with DM. Recent studies on the pathogenesis of HAEC suggest that susceptibility to HAEC in patients with DS is partly due to impaired immune function of the intestinal mucosa, in particular impaired intestinal B-cell function and impaired production IgA.23–26. This dysfunction probably results in an inability to respond to infectious lesions, predisposing the patient to bacterial invasion and HEC. Children with DS have a well-described predisposition to many infectious diseases and cancers, and specific studies have shown that patients with DS have an initial deficiency in both humoral and cellular immunity, resulting in profound B-lymphocytopenia and alterations in IgA production [3, 11].

CONCLUSION

It is clear that children with DS suffering from symptoms such as constipation, abdominal bloating, regurgitation and vomiting during the newborn period and the first months of life should not receive conservative treatment before HD is excluded with the help of rectal biopsy. Earlier diagnosis may help to reduce the proportion of decompensated forms of the disease and reduce the risk of complications.

Given the higher risk of CRA failure in patients with diabetes, obesity, immunological disorders and other additional risk factors, preventive stomas or two-stage interventions should be more widely used in relegation surgery, which may significantly reduce the risk of inflammatory complications in the postoperative period.

The high incidence of CRA failure may be due to ischemic disorders in the lowered intestine associated with the peculiarities of angioarchitectonics in patients with DS. The use of hyperbaric oxygenation in the early postoperative period may be a promising way to prevent ischemic complications in patients of this group.

Patients with diabetes and HD should be examined to exclude immunological disorders, as the presence of the latter may lead to the development of life-threatening complications after surgery.

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.

Funding source. This study was not supported by any external sources of funding.

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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UDC [616.329-002-085+611.329-092+616.33-008.17]-053.3-07-08
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DRAFT CLINICAL RECOMMENDATIONS FOR NEONATOLOGISTS AND PEDIATRICIANS ON THE DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE IN NEWBORNS (FOR DISCUSSION BY SPECIALISTS)

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For citation: Ivanov DO, Novikova VP, Gurova MM, Zavyalova AN, Panchenko AS, Privorotsky VF, Fedorova LA, Balashova EN, Khavkin AI. Draft clinical recommendations for neonatologists and pediatricians on the diagnosis and treatment of gastroesophageal reflux disease in newborns (for discussion by specialists). Children's Medicine of the North-West. 2024;12(3):173–183. DOI: https://doi.org/10.56871/CmN-W.2024.19.24.021

Received: 09.07.2024 **Revised: 14.06.2024** **Accepted: 10.09.2024**

Abstract. Clinical recommendations are intended to optimize the tactics of managing newborns with gastroesophageal reflux disease and are offered for use by pediatricians working in outpatient and inpatient healthcare of the Russian Federation, aimed at providing information support pediatricians, neonatologists and gastroenterologists and all specialists interested in neonatology and medical clinical gastroenterology. These recommendations are offered for public discussion and are posted in full on the website (https://neonatology.pro).

Keywords: *newborns, gastroesophageal reflux disease, diagnostics, treatment, clinical recommendations*

ПРОЕКТ КЛИНИЧЕСКИХ РЕКОМЕНДАЦИЙ ДЛЯ НЕОНАТОЛОГОВ И ПЕДИАТРОВ ПО ДИАГНОСТИКЕ И ЛЕЧЕНИЮ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ НОВОРОЖДЕННЫХ (ДЛЯ ОБСУЖДЕНИЯ СПЕЦИАЛИСТАМИ)

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Для цитирования: Иванов Д.О., Новикова В.П., Гурова М.М., Завьялова А.Н., Панченко А.С., Приворотский В.Ф., Федорова Л.А., Балашова Е.Н., Хавкин А.И. Проект клинических рекомендаций для неонатологов и педиатров по диагностике и лечению гастроэзофагеальной рефлюксной болезни новорожденных (для обсуждения специалистами) // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 173–183. DOI: https://doi.org/10.56871/CmN-W.2024.19.24.021

Поступила: 09.07.2024 **Одобрена: 14.06.2024** **Принята к печати: 10.09.2024**

Резюме. Клинические рекомендации предназначены для оптимизации тактики ведения новорожденных с гастроэзофагеальной рефлюксной болезнью и предлагаются к использованию врачам-педиатрам,

работающим в амбулаторном и стационарном звеньях здравоохранения РФ, направлены на обеспечение информационной поддержки врачей-педиатров, неонатологов, гастроэнтерологов и всех специалистов, интересующихся вопросами неонатологии и врачебной клинической гастроэнтерологии. Настоящие рекомендации предлагаются к обсуждению общественности и в полном виде размещены на сайте Российского общества неонатологов (https://neonatology.pro).

***Ключевые слова*:** *новорожденные, гастроэзофагеальная рефлюксная болезнь, диагностика, лечение, клинические рекомендации*

DEFINITION

Gastresophageal reflux disease (GERD) is a pathological condition that develops when gastric contents are thrown into the esophagus resulting in bothersome symptoms and/or complications [1, 2].

Features of the International Statistical Classification of Diseases and Related Health Problems 10th revision coding of the disease are as follows:

P78.8 Other specified disorders of the digestive system in the perinatal period.

EPIDEMIOLOGY

The true incidence of GERD in neonates is unknown, as in most cases the disease occurs in a mild form under the mask of infantile regurgitation related to functional gastrointestinal (GI) disorders [3]. At the same time, GERD is detected among 1 in 10 newborns admitted to the neonatal intensive care unit (NICU). A confirmed diagnosis of GERD leads to increased duration and cost of hospitalization [3].

ETIOLOGY AND PATHOGENESIS OF DISEASE

GERD is a multifactorial disease resulted in the passage of gastric contents into the esophagus — gastresophageal reflux (GER) [2, 3], characterized by a pathologically high frequency and/or duration of episodes, resulting in disruption of the integrity of the esophageal mucosa (OM) or esophageal barrier. In most cases, GER is not accompanied by clinical symptoms and is considered physiological in newborn infants [4].

Maintaining the integrity of OM is determined by the balance between the factors of "aggression" and OM ability to resist damaging effects of gastric contents ingested during GER.

Traditional "aggression" factors include: hydrochloric acid, in case of duodenogastric reflux — lysolecithin, bile acids, pancreatic juice enzymes. However, these factors do not play such a role in the newborn period as they do in subsequent age periods, which is due to anatomic-physiological features [4].

Protective factors are represented by the anti-reflux barrier (lower esophageal sphincter and diaphragm legs), esophageal OM resistance (pre-epithelial, epithelial and post-epithelial levels), esophageal clearance (pH recovery in the distal esophagus after each reflux episode) and timely evacuation of gastric contents [5].

The neonatal period is characterized by a decrease in the effectiveness of defense factors with an unchanged level of aggression factors [3, 6].

Risk factors for the development of neonatal GERD are shown in Table 1 [3].

Main mechanisms in the pathogenesis of GERD development

1. Pathological transient relaxation of the lower esophageal sphincter (LOS), impairing the functioning of the anti-reflux barrier.

Intermittent relaxation of the LOS that occurs during swallowing is physiological and usually does not impair esophageal clearance. Pathological transient LOS relaxation (TLOSR), unrelated to swallowing, characterized by high frequency and/or duration of LOS relaxation episodes, underlies the development of neonatal GERD [7]. Triggers of pathological LOS relaxation are [7, 8]:

- abdominal bloating;
- tension of the anterior abdominal wall of the stomach;
- respiratory distress syndrome;
- therapy with xanthine derivatives (ATX code N06BC).

2. Changes in the abdominal-thoracic pressure gradient.

The lower pressure in the thoracic cavity compared to the abdominal cavity creates a pressure gradient that promotes retrograde flow of gastric contents from the stomach into the esophagus. Any conditions that increase this gradient increase the likelihood of GER [7, 9].

Among the conditions associated with GERD in the newborn period as triggers are:

1) apnea of premature neonates [10, 11];
2) bronchopulmonary dysplasia [12, 13].

Table 1. Risk factors for the development of GERD in the neonatal period

Таблица 1. Факторы риска развития ГЭРБ в периоде новорожденности

Краниофациальные аномалии / Craniofacial anomalies	Хейлосхизис / Cheiloschisis
Аномалии развития дыхательных путей / Anomalies of the respiratory tract	Трахеоэзофагеальная фистула / Tracheoesophageal fistula
Аномалии развития диафрагмы / Developmental abnormalities of the diaphragm	• Врожденная диафрагмальная грыжа / Congenital diaphragmatic hernia • Грыжа пищеводного отверстия диафрагмы / Hiatal hernia
Аномалии развития передней брюшной стенки / Developmental anomalies of the anterior abdominal wall	Дефекты брюшной стенки / Abdominal wall defects
Аномалии желудочно-кишечного тракта / Developmental and congenital anomalies of the gastrointestinal tract	• Атрезия пищевода / Esophageal atresia • Аномалии поворота кишечной трубки / Anomalies of intestinal malrotation • Стеноз пилорического отдела / Pyloric stenosis • Атрезия двенадцатиперстной кишки и других отделов тонкой кишки / Atresia of the duodenum and other parts of the small intestine • Стриктуры кишечника / Intestinal strictures • Кольцевидная поджелудочная железа / Annular pancreas
Патология нервной системы / Pathology of the central nervous system	• Внутрижелудочковые кровоизлияния / Intraventricular hemorrhages • Перивентрикулярная лейкомаляция / Periventricular leukomalacia • Гипоксически-ишемическая энцефалопатия / Hypoxic-ischemic encephalopathy

The causes of such a relationship may be due to chronic aspiration of gastric contents and increased intra-abdominal pressure as a result of respiratory distress, which in turn may lead to increased reflux. However, available studies aimed at identifying the relationship between the above conditions have a low evidence level [3].

CLASSIFICATION

A working classification of GERD in neonates is presented [14].

I–IV degrees of GERD with esophagitis are distinguished on the basis of the severity of endoscopic changes in EM:

I degree — moderately pronounced focal erythema and/or friability of the abdominal esophageal mucosa;

II degree — total hyperemia of the abdominal esophagus with focal fibrinous plaque and possible single superficial, non-adherent erosions within the abdominal esophagus;

III degree — spread of inflammation and erosions (non-adherent or adherent but not circular) to the thoracic esophagus; increased contact vulnerability of the mucosa is possible;

IV degree — esophageal ulcer/ulcers, esophageal stenosis.

CLINICAL PICTURE

The clinical presentation is variable and nonspecific. Most of the suspected symptoms of GERD in the newborn period are unreliable, making GERD a diagnosis of exclusion. The following symptoms help to suspect the disease [3, 15]:

1) general manifestations — prolonged episodes of crying and restlessness, including night, low weight gain;
2) digestive system — regurgitation, vomiting, restlessness during feeding, hematemesis, refusal to eat [2];
3) respiratory system — cough that increases during feeding, stridor, wheezing or aspiration episodes;
4) cardiovascular system — apnea, bradycardia, decreased blood saturation.

In most cases, mild or moderate severity of symptoms is characteristic, manifested as episodes of restlessness, crying and deterioration of the quality of night sleep [3, 15].

DISEASE DIAGNOSIS

Criteria for establishing a diagnosis/condition

The following data are considered to establish the diagnosis:

Identification of risk factors for the development of GERD.

1. Nature of complaints — attention is paid to the time of regurgitation/vomiting, frequency, relationship to food intake, other complaints, additional presence of bile, blood in the contents, the rate of change in physical development indicators.
2. Physical examination — assessment of physical development, detection of anxiety symptoms.
3. Instrumental examination (esophagogastroduodenoscopy (EGDS), intraesophageally pH-metry, pH-impedanceometry).

Due to the absence of specific symptoms that are characteristic for GERD, it is necessary to pay attention to the presence of anxiety symptoms for differential diagnosis and identification of diseases with a similar clinical picture to GERD (Table 2).

Complaints and history

When GERD is suspected in a neonate, it is **recommended to:**

- Study the course of the early neonatal period to identify risk factors for the development of GERD;
- Note the time of debut and the dynamics of complaints [1–3, 5, 14].

Grade of recommendation — C (evidence level — 5).

Comments. *See "Etiology and pathogenesis of the disease". When studying the history of a newborn with suspected GERD, attention should be paid to to certain groups of patients (see Table 1) [3]. The most characteristic complaints include frequent regurgitation/vomiting accompanied by marked restlessness, sleep disturbance and decreased weight gain.*

Physical examination

A visual physical examination **is recommended** for a newborn with suspected GERD [3].

Grade of recommendation — C (evidence level — 5).

Comments*. See "Clinical presentation of the disease". Due to the absence of pathognomonic symptoms, first of all, it is necessary to pay attention to anxiety symptoms (see Table 2). In order to detect them it is necessary to carry out differential diagnosis with other pathological conditions that are similar to GERD.*

Table 2. Complaints and symptoms of concern ("red flags"), the presence of which requires the exclusion of diseases that have a similar clinical picture to GERD [2]

Таблица 2. Жалобы и симптомы тревоги («красные флаги»), наличие которых требует исключения заболеваний, имеющих сходную с ГЭРБ клиническую картину [2]

Жалобы / Complaints	Симптомы, выявленные при осмотре / Symptoms revealed during examination
Время появления регургитации <2 недель жизни / Time of onset of regurgitation <2 weeks of age	Отклонения от нормы, выявленные при общем осмотре, со стороны пищеварительной, дыхательной и нервной системы / Deviations from the normal state, revealed during a general examination, of the digestive, respiratory and nervous systems
Рвота с примесью желчи, ночная или постоянная рвота / Vomiting with bile, nokturnal or constant vomiting	Выраженное вздутие живота / Severe abdominal distension
Хроническая диарея или диарея с кровью / Chronic diarrhea or bloody diarrhea	Лихорадка / Fever
Гематомезис / Hematemesis	Вялость или повышенное беспокойство / Weakness or increased restlessness
Дизурия / Dysuria	Плохие прибавки или отсутствие прибавок массы тела / Poor or no weight gain
Судороги / Cramps	Выбухание большого родничка или быстрый прирост окружности головы или микро/макроцефалия / Bulging of the anterior fontanelle or rapid increase in head circumference or micro/macrocephaly
Рецидивирующая пневмония / Recurrent pneumonia	Патологические изменения мышечного тонуса / Pathological changes in muscle tone
Дисфагия / Dysphagia	Отклонения в психомоторном развитии / Deviations in psychomotor development

Note. The appearance of regurgitation in the 1st-2nd week of life requires the exclusion of infectious diseases, anatomical anomalies, and metabolic disorders.

Примечание. Появление регургитации на 1-2-й неделе жизни требует исключения инфекционных заболеваний, анатомических аномалий, метаболических нарушений.

Laboratory diagnostic tests

- It is **recommended** that all newborn infants with suspected GERD and complaints of vomiting and poor weight gain should undergo a complete blood test to exclude the infectious nature of symptoms and to identify associated conditions/complications such as anemia [16].
  Grade of recommendation — C (evidence level — 5).
  Comments. *Exclusion of infectious diseases is necessary at the debut of symptoms which are typical for GERD in the first week of the child's life [2].*
- It is **recommended** that newborn infants with suspected GERD with complaints of intense vomiting and poor weight gain should undergo a study of acid-base status (ABS) and blood gas composition, determination of lactic acid and ammonia levels in the blood to identify signs of metabolic disorders for further diagnostic search [16].
  Grade of recommendation — C (evidence level — 5).
  Comments. *Exclusion of metabolic abnormalities is required at the onset of complaints which are typical for GERD in the first week of life [2].*

Instrumental diagnostic tests

- Esophagogastroduodenoscopy is **recommended** for neonates with suspected GERD in order to determine the degree of esophageal mucosa lesions, as well as to detect complications and to perform differential diagnosis [17].
  Grade of recommendation — C (evidence level — 5).
  Comments. *The study evaluates the condition of the esophageal mucosa, which is especially important if there are alarming symptoms such as hematemesis, dysphagia, delayed weight gain or anemia, in order to detect complications of GERD, such as erosive esophagitis [2, 17].*
  The examination allows diagnosing a number of congenital esophageal anomalies (atresia, stenosis, 'short esophagus', etc.), as well as acquired diseases of inflammatory and non-inflammatory genesis.
- Newborns with GERD **are recommended** to undergo esophageal biopsy by endoscopy followed by pathological and anatomical examination of esophageal biopsy (surgical) material in case there is no effect from the current therapy in order to exclude rare esophageal diseases, such as eosinophilic esophagitis [2, 3].
  Grade of recommendation — C (evidence level — 5).
  Comments. *It is important to note that even small deviations in biopsy technique affect the validity of histology as a diagnostic method identifying reflux esophagitis. At least two biopsy specimens (preferably four) should be taken at a distance of 2 cm or more above the Z-line for a reliable diagnosis [18].*
  The diagnostic value of biopsy is increased if there are alarm symptoms such as hematemesis, swallowing disorders, anemia. Biopsy is useful to detect complications of GERD such as erosive esophagitis, strictures, or to diagnose conditions that may mimic GERD such as eosinophilic esophagitis [2, 17].
- It is **recommended** that newborns with GERD undergo daily intraesophageally pH-metry in case current therapy is not effective [2, 3, 6, 14, 19].
  Grade of recommendation — C (evidence level — 5).
  Comments. *This method allows to accurately determine the acidic gastric content throwing into the esophagus and to estimate its duration. The study usually lasts from several hours to several days, after which the reflux index (RI) is calculated. The reflux index is defined as the percentage of pH recording time less than 4 to the total study time (in %) [14, 19]. Limitations of pH monitoring in neonates include the lack of reference pH values in this age group and the inability to detect weakly acidic refluxate, which makes up the majority of refluxates in infants (up to 73% of reflux episodes are weakly acidic and alkaline, with pH between 4 and 7, which is largely determined by nutritional characteristics — the alkaline pH of breast milk) [4, 6].*
- Daily pH-impedanceometry is **recommended** for newborns with GERD in case there is no effect on the therapy to correct it [3, 19].
  Grade of recommendation — C (evidence level — 5).
  Comments. *PH-impedanceometry allows to overcome the limitation of the daily pH-metry and to detect both acid and non-acid reflux. Additionally, the method can determine the height of refluxate throw into the esophagus and predict*

the risk of refluxate aspiration. Combined pH-impedance monitoring is promising as an objective method for diagnosing GERD, but more normative data are required before this method can be considered the 'gold standard' test [3, 19].

- It is **recommended** to perform esophageal fluoroscopy with contrast for differential diagnosis and exclusion of anatomical anomalies in newborns with GERD with suspected esophageal orifice hernia, diaphragmatic hernia, refractory course of GERD (absence of convincing clinical and endoscopic remission during 4–8 weeks of therapy) [2, 17].

  Grade of recommendation — C (evidence level — 5).

  Comments. *Barium examination of the esophagus and stomach is performed in straight and lateral projections and in Trendelenburg position with slight compression of the abdominal cavity. The permeability of suspension, the diameter of the esophagus, contours, elasticity of the walls, pathological constrictions, ampullary dilatations, peristalsis, relief of the mucosa are assessed during the study. In case of obvious reflux, the esophagus and stomach radiologically form the figure of "elephant with raised trunk". Delayed radiographs again show the contrast agent, which confirms the fact of reflux. This method is important in the diagnosis of sliding hernia of the esophageal aperture of the diaphragm (SHOAD), anomalies of esophageal development, assessment of consequences of trauma and surgical interventions. The method is also irreplaceable in the diagnosis of functional esophageal diseases. According to the literature, the specificity of radiological examination in the diagnosis of SHOAD is 94% [17].*

  Disadvantages of the method include the fact that radiography does not always allow fixation of hernias of small size, and also gives a high radiation load [2, 17].

Other diagnostic tests

Diagnosis of diseases associated with GERD is performed if there are indications [3].

TREATMENT

Taking into account the multicomponent nature of this pathophysiological phenomenon, GERD therapy is complex. It includes dietary therapy, postural, drug and non-drug therapy, surgical correction ('step therapy'). The choice of treatment method or their combination is carried out depending on the causes of reflux, its degree and spectrum of complications [2, 14].

Therapeutic measures in GERD are based on three main provisions:

1) a complex of non-pharmacological actions, mainly normalization of lifestyle, daily regime and diet;
2) conservative therapy;
3) surgical correction.

Conservative treatment

Diet therapy

- Postural therapy or treatment by changing the body position is **recommended** in newborns with GERD: when feeding, it is necessary to keep a child at an angle of 45–60°, which prevents regurgitation and aerophagia. At night, it is advisable to raise the head end of the bed by 10–15 cm [20]. Overfeeding of children with GERD is inadmissible [21].

  Grade of recommendation — C (evidence level — 5).

  Comments. *Abdominal and left-sided positions are not recommended for use at home because they increase the risk of sudden death syndrome [14, 22].*

- Dietary correction is **recommended,** when postural therapy is not effective. It includes anti-reflux milk mixtures with increased viscosity, they contain thickeners to reduce the frequency of regurgitation and vomiting [23].

  Grade of recommendations — C (evidence level- 5).

  Comments. *The use of specific foods enriched with complex carbohydrates to prevent backward movement of gastric contents and improve gastric emptying is a fundamental direction of dietary therapy of GERD in children. This nutritional approach is very effective for children with mild regurgitation and sufficient or slightly low rates of weight gain. When combined with postural therapy, its effectiveness reaches 90–95% [14, 23].*

  The best effect is achieved when anti-reflux mixtures are administered at the earliest stages of the disease.

  It should be remembered when prescribing mixtures with non-digestible polysaccharides (PS) (carob gum) as a thickener, that these mixtures are:

  - *therapeutic and should be prescribed by a doctor;*

- *require a clear calculation of the amount in the child's daily ration (1/2, 1/3 or 1/4);*
- *are prescribed for a limited period of time;*
- *are not recommended for healthy children who do not suffer from regurgitation;*
- *are only one component of a treatment program.*

Options for prescribing anti-reflux formulae:

- *At the end of each breast milk/adapted formula feeding, an anti-reflux (AR) formula is administered at 1/2–1/4 of the feeding volume;*
- *AR formula is administered 1–3 times a day in the volume of feedings, otherwise adapted formula is used;*
- *AR formula is administered in full daily volume for 2–4 weeks.*

- If dietary correction with anti-reflux milk mixtures is ineffective, it is **recommended** to use mixtures based on highly hydrolyzed protein or amino acid mixtures for two weeks [2, 23].
  Grade of recommendations — C (evidence level — 5).
  Comments. *Highly hydrolyzed protein-based mixtures are particularly indicated when a child has other symptoms that indicate atopic diseases, such as atopic dermatitis [2]. In case the clinical picture does not improve in two weeks, the chosen tactics of diet therapy is not effective. If there is a positive effect, it is recommended to continue taking the mixture for up to 12 months, but not less than 6 months [2, 24, 25].*

Pharmacological therapy

- Routine drug therapy **is not recommended** for newborns with uncomplicated GER because of insufficient efficacy and safety data; in most cases, infants' symptoms resolve on their own after 6 months of age [17].
  Grade of recommendation — C (evidence level — 5).
  Comments*. Available data do not support the efficacy of proton pump inhibitors (ATX code A02BC) for the treatment of GERD symptoms in neonates. Acid-suppressive therapy should not be used in preterm infants because of serious side effects [26, 27].*
- Therapy with proton pump inhibitors (code ATX A02BC) (IPN) — #esomeprazole** (code ATX A02BC05) is **recommended** for neonates with severe symptoms of GERD (restlessness, refusal to feed, poor weight gain) and moderate or severe esophagitis in case non-drugs methods of correction are not effective [3, 17].
  Grade of recommendation — C (evidence level — 5).
  Comments. *#Ezomeprazole** (ATX code A02BC05) is administered in a daily dose of 0.5 mg/kg for 1–2 intakes. The average duration of therapy is 4–6 weeks. Contraindications — individual intolerance to the drug [3, 17].*

Surgical treatment

- Neonates with GERD are **recommended** to undergo fundoplication / laparoscopic fundoplication (Nissen method, less frequently Tal, Dore, Toope methods) (open access fundoplication / laparoscopic fundoplication) in case of long-term persisting endoscopic picture of reflux esophagitis of III-IV degree on the background of repeated courses of therapy, in case of GERD complications (bleeding, strictures), in case of combination of GERD with SHOAD [28, 30].
  Grade of recommendation — C (evidence level — 5).
  Comments. *In the absence of contraindications, laparoscopic fundoplication is preferable [28].*

MEDICAL REHABILITATION AND HEALTH RESORT TREATMENT

Special methods of medical rehabilitation have not been developed.

PREVENTION AND MEDICAL FOLLOW-UP, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

To prevent GERD, it is recommended to limit/avoid factors that provoke the development of GERD [14]:

1) to avoid overfeeding;
2) if possible, to limit the use of medications that relax the lower esophageal sphincter.

- It is **recommended** that newborns diagnosed with GERD are monitored by a gastroenterologist [14, 29].
  Grade of recommendation — C (evidence level — 5).
  Comments. *Subsequent follow-up of a patient with GERD is performed at least twice a year for three years from the last visit [29], and is determined by the severity of clinical symptoms and clinical and endoscopic findings.*

ORGANISATION OF MEDICAL CARE

Children with GERD are observed by a paediatrician and a gastroenterologist, if there is

a concomitant pathology — together with relevant specialists, including a paediatric surgeon.

Indications for hospital admission include the onset of symptoms requiring urgent intervention (dysphagia, weight loss, hematemesis or recurrent vomiting) [30].

Discharge of a patient with GERD is indicated if a patient is in satisfactory condition, symptoms of GERD have resolved, and an endoscopic picture has improved/normalized.

After discharge from hospital, children should undergo medical follow-up by a paediatrician and a gastroenterologist [14].

As a rule, children with GERD usually do not need treatment in a 24-hour hospital, except for a complicated course and indications for surgical intervention. Hospitalization in a day hospital (average duration is 10–14 days) is appropriate to establish the diagnosis and possible correction of therapy.

COMPLICATIONS

A formidable complication of GERD are strictures of the esophagus, which arise with the scarring of ulcer defects. This process involves deep layers of the esophageal wall and peri-esophageal tissues against the background of chronic inflammation, i.e. perioesophagitis occurs. The predominance of fibrosis leads to scar formation, as a result a peptic stricture of the esophagus develops.

Another serious complication of GERD is posthemorrhagic anemia, which can occur both in case of sliding hernia of the esophageal aperture of the diaphragm, the impingement of which traumatizes the mucous membrane of the diaphragmatic 'sac', and as a result of erosive and ulcerative lesions of the esophageal mucosa.

DIFFERENTIAL DIAGNOSTICS OF GERD

Differential diagnosis of GERD is differentiated with the following diseases and conditions:

1) achalasia of the cardia;
2) esophageal narrowing caused by pathological changes in the neighboring organs;
3) mediastinal tumors and cysts;
4) posterior mediastinitis;
5) pleuropulmonary fibrosis;
6) aortic aneurysm;
7) right-sided aorta;
8) vascular anomalies;
9) drug exposure;
10) *congenital metabolic disorders:*
    a) disorders of organic acid metabolism;
    b) disorders of amino acid metabolism;
    c) primary lactate acid acidosis;
    d) fatty acid oxidation disorders.

OUTCOMES AND PROGNOSIS

Most children with GERD have a favorable prognosis. A number of complications, such as Barrett's esophagus, may develop only at an older age [14, 17].

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.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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UDC 616.053.2
DOI: 10.56871/CmN-W.2024.95.76.022

TRADITIONS, ACHIEVEMENTS, PROSPECTS OF THE DEPARTMENT OF PEDIATRICS AND CHILDREN'S CARDIOLOGY OF THE NWSMU NAMED AFTER I.I. MECHNIKOV. ON THE 120th ANNIVERSARY OF THE DEPARTMENT'S ESTABLISHMENT

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For citation: Melnikova IYu. Traditions, achievements, prospects of the Department of Pediatrics and Children's Cardiology of the NWSMU named after I.I. Mechnikov. On the 120th anniversary of the Department's Establishment. Children's Medicine of the North-West. 2024;12(3):184–191. DOI: https://doi.org/10.56871/CmN-W.2024.95.76.022

Received: 27.06.2024 **Revised: 12.08.2024** **Accepted: 10.09.2024**

Abstract. The article describes the 120-year history of the creation and development of the Department of Pediatrics and Pediatric Cardiology North-Western State Medical University named after I.I. Mechnikov. The historical aspects of the formation of pediatrics and pediatric cardiology are reflected through the activities of the heads of departments. It is noted that the practical orientation of all employees of the department is of particular value, and knowledge of the needs and requirements of practical healthcare contributes to the formation of the scientific direction of the department. Only the close relationship between the department and clinical bases provides the opportunity to integrate educational, clinical, scientific and innovative activities as a single pediatric school, so necessary for the development of domestic healthcare.

Keywords: *Department of Pediatrics and Pediatric Cardiology of the I.I. Mechnikov NWSMU, Russov A.A., Medovikov P.S., Shalkov N.A., Orlova N.V., Mutafyan O.A., pediatric school, jubilee*

ТРАДИЦИИ, ДОСТИЖЕНИЯ, ПЕРСПЕКТИВЫ КАФЕДРЫ ПЕДИАТРИИ И ДЕТСКОЙ КАРДИОЛОГИИ СЗГМУ ИМ. И.И. МЕЧНИКОВА. К 120-ЛЕТИЮ СО ДНЯ СОЗДАНИЯ КАФЕДРЫ

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Для цитирования: Мельникова И.Ю. Традиции, достижения, перспективы кафедры педиатрии и детской кардиологии СЗГМУ им. И.И. Мечникова. К 120-летию со дня создания кафедры // Children's Medicine of the North-West. 2024. Т. 12. № 3. С. 184–191. DOI: https://doi.org/10.56871/CmN-W.2024.95.76.022

Поступила: 27.06.2024 **Одобрена: 12.08.2024** **Принята к печати: 10.09.2024**

Резюме. В статье изложена 120-летняя история создания и развития кафедры педиатрии и детской кардиологии Северо-Западного государственного медицинского университета им. И.И. Мечникова. Отражены исторические аспекты становления педиатрии и детской кардиологии через деятельность заведующих кафедры. Отмечено, что особую ценность составляет практическая ориентированность всех сотрудников, а знание потребностей и требований практического здравоохранения способствует формированию научного направления кафедры. Только тесная взаимосвязь кафедры и клинических баз обеспечивает возможность интеграции образовательной, клинической, научной и инновационной деятельности как единой педиатрической школы, столь необходимой для развития отечественного здравоохранения.

Ключевые слова: *кафедра педиатрии и детской кардиологии СЗГМУ им. И.И. Мечникова, Руссов А.А., Медовиков П.С., Шалков Н.А., Орлова Н.В., Мутафьян О.А., педиатрическая школа, юбилей*

A teacher and a doctor are two professions for which love for people is an indispensable quality.

N.M. Amosov,
Corresponding Member of
the Russian Academy of Medical Sciences.

The connection of times is a living matter, let's take a walk on the route "Paediatrics of St. Petersburg — Leningrad — St. Petersburg". We will pass through epochs. Sometimes only a part of an event is preserved in the memory, but like a tip of a ball of thread that can lead to the depth of time. When you name your contemporaries and remember your mentors, memory will tell you the names and patronymics of their teachers. The chain stretches without a break, and it extends for centuries!

The Department of Paediatrics and Paediatric Cardiology (Head of the Department — Doctor of Medical Sciences, Professor I.Y. Melnikova) of the I.I. Mechnikov North-West State Medical University (NWSMU) was organized in 2011 by merging two independent institutions — St. Petersburg Medical Academy of Postgraduate Education (SPbMAPO) and St. Petersburg State Medical Academy named after I.I. Mechnikov. At the same time, the name of the department was changed due to three reasons: firstly, the urgent need to improve the qualification of paediatricians on topical issues of paediatric cardiology; secondly, the fact that scientific interests of a number of the department's staff are focused on the problem of cardiology; thirdly, teaching paediatric cardiology is a long-standing tradition of this departmental team.

The history of the department reflects the difficult history of our country, which manifested itself in its repeated reorganization in accordance with requirements of the time. The political events that took place in our country during the XX and the first decade of the XXI century, have left an imprint on the history of the department.

Let us outline the main historical milestones, going back in time. The Department of Paediatrics and Paediatric Cardiology of I.I. Mechnikov NWSMU is the successor of the Department of Paediatrics N 1 of SPbMAPO (since 1998), earlier — LenGIDUV (since 1924), which, in its turn, was the successor of the Department of Paediatrics of the Eleninsky Clinical Institute (since 1917), and before that — the Department of Paediatrics of the Imperial Clinical Institute of the Grand Duchess Elena Pavlovna.

At the end of the XIX century, paediatrics was not an independent medical discipline, and the specialty of paediatrician did not officially exist. Despite the fact that the oldest Russian department of paediatric diseases named after M.S. Maslov at the Military Medical Academy in S.M. Kirov Military Medical Academy (formerly the Medical and Surgical Academy) was the first in Russia, it did not prepare future paediatrics. At that time it was possible to become a paediatrician only within the framework of postgraduate education.

The Clinical Institute of the Grand Duchess Elena Pavlovna was opened in St. Petersburg in May 1885 (in old style, 3 June in new style) on the initiative of the famous general practitioner, professor, physician in ordinary E.E. Eichwald (1837–1889). The Clinical Institute was established for scientific research and scientific and practical improvement of Russian doctors in various specialties.

The course on children's diseases began in autumn 1885. Famous physicians were invited to teach zemskiy doctors, among them were MD, V.N. Reitz, director of the Elizabeth Clinical Hospital for Young Children, and Doctor of Medicine K.A. Raukhfus, director of the Prince Peter Oldenburgsky Children's Hospital (since 1919 — the K.A. Raukhfus Children's City Hospital N 19 named after Dr. K.A. Raukhfus, since 2019 — the Children's City Hospital No. 19., since 2019 — SPbGBUZ Children's City Multidisciplinary Clinical Centre of High Medical Technologies named after K.A. Raukhfus, Chief Medical Officer — Doctor of Medical Sciences, V.Y. Detkov).

The hospital headed by K.A. Raukhfus was the center of scientific medical thought. In 1904, under these unique conditions, the Department of Paediatrics at the Imperial Clinical Institute was established. The Institute was headed by Professor Alexander Andreyevich Russov, a successor of Professor V.N. Reitz as chief physician of the Elizabethan Children's Hospital, then by Dr K.A. Raukhfus as chief physician of the Prince P. Oldenburgsky Hospital. Later the department was headed by remarkable paediatric scientists who left a rich legacy in the field of science and teaching methods. Until 1933 the department was headed by Professor P.S. Medovikov. From 1933 to 1952 the Department of Paediatrics of Leningrad University of Pediatrics was transferred to LPMI under the supervision of Professor E.I. Fridman, and from 1945 — Professor, Academician of the Academy of Medical Sciences of the USSR M.S. Maslov. After the return of the Pediatrics Department N 1 in 1957 to Leningrad University of Pediatrics, it was headed by Professor N.A. Shalkov, who was a col-

ISSN 2221-2582

league of Professor M.S. Maslov at the Department of Pediatrics of the Kirov Military Medical Academy, where he defended his doctoral thesis on "External respiration in healthy and sick children". The materials of this thesis formed the basis of his monograph "Issues of Physiology and Pathology of Respiration in Children" (1957). Having headed the department, N.A. Shalkov widely unfolded scientific research on physiology and pathology of respiration and blood circulation in children. Under his supervision 18 candidate dissertations and 1 doctoral thesis were carried out.

In addition to the cycles held for local paediatricians, heads of departments of children's hospitals and polyclinics, Professor N.A. Shalkov proposed to hold cycles on paediatric cardiorheumatology and pulmonology.

The first cycle "Cardiology and Rheumatology in Children" in our country was conducted by the staff of the Department of Paediatrics N 1 in 1965. Since 1967 the Department began to conduct field cycles of advanced training in paediatrics, on pathology of children of early and older age, on cardiology and rheumatology (in Barnaul, Vologda, Arkhangelsk, etc.).

Professor N.A. Shalkov organized consultative assistance to various medical institutions of practical health care in Leningrad and the region: in particular, to the children's department of the Central Regional Hospital of Gatchina, the children's pulmonary department in Kolchanovo, the children's cardiology and rheumatological sanatorium "Trudovye Reserves" of the North-West Administration of health resorts of the USSR, as well as to a number of children's polyclinics in the city and the region.

From 1974 to 1996, the Department of Paediatrics N 1 was headed by Professor, Honored Worker of Science of the Russian Federation Nina Vasilievna Orlova, a student and follower of N.A. Shalkov's ideas in the field of physiology and pathology of cardiovascular and respiratory systems in children. In 1975, N.V. Orlova defended her doctoral thesis "The interrelation and interdependence of changes in heart and vascular functioning of children with rheumatism", in 1977 she was awarded the degree of Doctor of Medical Sciences, and in 1978 she was awarded the academic title of Professor. N.V. Orlova always considered that the most important duty of the department was professional training of doctors in different branches of the health care system, including interns and clinical residents, so she paid special attention to the organization of educational processes.

At the end of 1975, N.V. Orlova organized advanced training cycles on clinical electrocardiography in children.

Fig. 1. Head of the Department, Professor I.Yu. Melnikova

Рис. 1. Заведующая кафедрой, профессор И.Ю. Мельникова

Fig. 2. Corresponding Member of the Russian Academy of Sciences, Professor R.R. Movsesyan

Рис. 2. Член-корреспондент РАН, профессор Р.Р. Мовсесян

120-ЛЕТНЯЯ ИСТОРИЯ КАФЕДРЫ

Кафедра педиатрии и детской кардиологии

КЛИНИЧЕСКИЙ ИНСТИТУТ ВЕЛИКОЙ КНЯГИНИ ЕЛЕНЫ ПАВЛОВНЫ

В.Н. Рейтц

К.А. Раухфус

А.А. Руссов

П.С. Медовиков

Н.А. Шалков

Н.В. Орлова

О.А. Мутафьян

Fig. 3. History of the department

Рис. 3. История кафедры

From 1996 to 2004, the department was headed by Professor Oleg Amayakovich Mutafyan, who was a student of N.A. Shalkov and the author of more than 110 scientific papers, mainly devoted to the issues of paediatric cardiology. Five PhD theses were defended under his scientific supervision. His books include "Carditis in Children and Adolescents", "Paediatric Cardiology", "Heart Defects in Children and Adolescents", "Emergency Cardiology of Children and Adolescents". They are devoted to topics which are considered to be very difficult for paediatricians.

Since 2005, the Department of Paediatrics N 1 (renamed the Department of Paediatrics and Paediatric Cardiology of the I.I. Mechnikov North-Western State Medical University in 2010) has been headed by Doctor of Medical Sciences, Professor Irina Yurievna Melnikova (Fig. 1). Formulating tasks and requirements for the staff, she tirelessly emphasizes that it is important to observe the leading university principle — the scientific imperative, which should permeate all aspects of departmental activity, without which the educational process easily degenerates into scholasticism.

Traditions of the department are ensured by 120-year history and highly professional team of like-minded people (Fig. 3), which consists of 5 professors, 7 associate professors, 9 assistants and 3 laboratory assistants. The staff of the department includes Ruben Rudolfovich Movsesyan, the Chief Consultants paediatric cardiac surgeon of the St. Petersburg Health Care Committee, Doctor of Medical Sciences, Professor, Corresponding Member of the Russian Academy of Sciences, Head of the Cardiac Surgery Department of the St. Petersburg DGMCCC VMT (Fig. 2). The department focuses on providing medical care to children with complex heart pathology. For 25 years more than 10,000 operations have been performed here and unique experience in surgical treatment of patients with extremely low birth weight has been accumulated. Ruben Rudolfovich personally performed more than 2500 operations, among them many unique ones conducted with thermal imaging control. R.R. Movsesyan performed a number of corrections for the first time: atrioventricular valve prosthetics using frameless mitral homografts; cone reconstruction in patients with Ebstein's anomaly in the first months of life, Norwood-Sanno operation with homograft; correction of coarctation of the aorta in patients with body weight less than 800 g; arterial switch operation and Norwood operation in patients with body weight less than 1600 g. Ruben Rudolfovich generously shares his unique experience with clinical residents, physicians, and students of the Faculty of Paediatrics. Seven PhD theses were defended under his scientific supervision.

ISSN 2221-2582

The direction of cardiology and cardio-rheumatology at the department was headed by Professor Vladimir Vladimirovich Yuryev from 2010 to 2014, he gave lectures to doctors and carried out therapeutic and advisory activities. He wrote 225 papers on the pathology of early childhood and topical issues of paediatric cardiology and rheumatology. Professor V.V. Yuryev was the chief paediatric cardiologist-rheumatologist of Leningrad and the Leningrad region for more than 15 years. Since 2014, Vitolda Ivanovna Belyakova, PhD in MS, was one of the first to study the clinical and immunological features of the course of acute rheumatic fever in children in our country. She participated in the pedagogical process at the department for two years. Today the cardiological direction at the department is supervised by Dr. R.R. Movsesyan, Doctor of Medical Sciences, Professor, Corresponding Member of the Russian Academy of Sciences, Head of the department; I.Yu. Melnikova, PhD of Medical Sciences, Professor; S.N. Chuprova, PhD of Medical Sciences, Associate Professor; pulmonological direction: E.G. Khramtsova, Associate Professor; S.V. Starevskaya, Doctor of Medical Sciences, Associate Professor; assistants S.I. Melnik, I.O. Shmeleva; adolescent medicine — A.M. Kulikov, Doctor of Medical Sciences, Professor.

Within the first years after the organization of I.I. Mechnikov NWSMU, the Department had to revise and optimize the teaching and methodological process in accordance with new requirements of the University management. In particular, a curriculum for the new officially introduced specialty "Paediatric Cardiology" was developed and approved.

The department was one of the first in the Russian Federation to start professional retraining of doctors in the specialty "Paediatric Cardiology". A two-year residency "Paediatric Cardiology" was introduced for the first time. A notable feature of additional professional education (APE) at the department is the variety of disciplines taught. Educational programs cover the whole spectrum of modern paediatrics: from neonatology to adolescent medicine. In addition to paediatrics itself, practical doctors have the opportunity to improve their competence in paediatric cardiology, pulmonology and functional diagnostics. Thematic cycles of continuing medical education address the issues of early childhood, nutrition of children of different ages, paediatric pulmonology, gastroenterology, nephrology, cardiology, adolescent medicine, adolescent reproductive health and clinical genetics. Such a wide range of opportunities of the department in the system of APE is based on a highly professional and versatile staff.

It is significant that some of the educational programs of the NMO are actually author's, as they

Fig. 4. Head of the Department Professor I.Yu. Melnikova and Professor V.N. Buryak with clinical residents at the DGMTC VMT named after K.A. Raukhfus

Рис. 4. Заведующая кафедрой профессор И.Ю. Мельникова и профессор В.Н. Буряк с клиническими ординаторами в ДГМКЦ ВМТ им. К.А. Раухфуса

Fig. 5. Professor's round

Рис. 5. Профессорский обход

include their own textbooks, monographs, manuals, and study guides which have been published by the department's staff in recent years .

Special attention has always been paid to the methodology of teaching. The experience of the department was reflected in the manual "Didactics and competence in the professional activity of a teacher of a medical university". In 2011, a cycle on the methodology of teaching adolescent medicine was held in cooperation with the Faculty of Medicine of the University of Lausanne (Switzerland). The simulated patient methodology was applied for the first time in the practice of the department.

Today, the staff implements training programs for advanced training and professional upgrading of paediatricians, paediatric cardiologists and other specialists in child and adolescent health care, as well as specialty programs in "Medicine" (4th year students of the Faculty of Medicine), bachelor's degree in "Nursing", clinical residency in "Paediatrics" and "Paediatric Cardiology" and postgraduate studies in "Paediatrics". Since 2020, the department has developed and implemented a training program for students of the Faculty of Paediatrics on the specialty "Paediatrics".

The Department does not have a paediatric clinic at the University, but it actively cooperates with modern unique clinical bases: Children's City General Hospital of Hight Medical Technologies (CCGH HMT) named after K.A. Raukhfus, Children's City Hospital of St. Mary Magdalene, Children's City Hospital N 3, Children's City Hospital named after N.F. Filatov, Children's Pulmonology Centre of St. Petersburg Research Institute of Phthisiology and Pulmonology (Fig. 4). Chief physicians (E.V. Plotnikova, Doctor of Medecine, Dr. V.Yu. Detkov, Honored Physician of the Russian Federation, A.G. Mikava, PhD in Medical Sciences, , K.A. Papayan, L.N. Isankina, Honored Physician of the Russian Federation, P.K. Yablonsky) understand and appreciate the necessity of mutual beneficial connection of practical health care and the department.

The Student Scientific Society (SSS) (supervisor — PhD in Medical Sciences, Associate Professor E.G. Khramtsova) is actively working at the department. The main direction of SSS: study of multidisciplinary aspects of paediatrics, the influence of infectious diseases on the cardiovascular system, the study of rare hereditary diseases with heart and kidney damage based clinical cases. Gastroenterological pathology, paediatric aspects of socially significant diseases (tuberculosis, arterial hypertension) are also among the subjects of study.

Special attention is paid to work with clinical residents. Residents are trained at the department on two basic educational programs — "Pediatrics" (supervisor — assistant of the department S.I. Melnik) and "Children's cardiology" (supervisor — Doctor of medical sciences, prof. V.N. Buryak). Residents take an active part in clinical analyses, present patient case histories, participate in joint research work with physicians of clinical bases under the guidance of faculty members of the department (Fig. 5).

In 2019, Children's Clinical and Diagnostic Centre was opened in at the Medical and Preventive Centre of the Mechnikov Northwestern State Medical University (Professor I.Yu. Melnikova is the Head of the Centre). This allowed to expand the educational process, to conduct federal interdisciplinary consultations with geneticist, Dr. V.I. Larionova in different regions of the Russian Federation (Kaluga Region, Samara, Stavropol Territory, Tomsk, Leningrad Region), to diagnose and solve questions on the tactics of managing patients with such complex diseases as tyrosinemia, fatty acid metabolism disorders, sphingolipidosis:

ISSN 2221-2582

Fig. 6. Department staff, from left to right: bottom row — Assoc. Prof. V.Yu. Chistyakova, Head department Prof. I.Yu. Melnikova, Prof. V.N. Buryak, Assoc. Prof. E.G. Khramtsova, second row — Prof. A.M. Kulikov, Ass. I.O. Shmeleva, Assoc. Prof. T.D. Loskucheryavaya, Assoc. Prof. N.E. Luppova, Assoc. Prof. O.V. Ryabykh

Рис. 6. Коллектив кафедры, слева направо: нижний ряд — доц. В.Ю. Чистякова, зав. кафедрой проф. И.Ю. Мельникова, проф. В.Н. Буряк, доц. Е.Г. Храмцова, второй ряд — проф. А.М. Куликов, асс. И.О. Шмелева, доц. Т.Д. Лоскучерявая, доц. Н.Е. Луппова, доц. О.В. Рябых

Fabry disease (Fabry-Anderson), Niemann–Pick disease, homocystinuria (remethylation defect) in order to solve the issue of Cystadane therapy prolongation.

An important area of the department's work is educational activities among patients' parents. For this purpose, since 2020 the Department has been running the "School of Paediatrics" and "School of Pulmonology, Allergology" (supervisor — assistant S.I. Melnik). Using social networking sites, the department staff answer patients' questions related to treatment and vaccination, inform about the peculiarities of diagnostic search, nuances of nebulizer therapy and skin care for patients with atopy. The audience of the groups "School of Paediatrics", "School of Pulmonology, Allergology", located not only in different cities, but also in different countries. Parents can get answers to their questions, which often arise after the end of a doctor's appointment. Keeping a patient and treating physician connected allows to increase compliance to treatment.

Scientific work is carried out within the framework of the complex theme "Development of modern technologies of preservation, development and restoration of reproductive health of women, newborns, children and adolescents for creation and introduction of innovative products" and includes several directions: cardiosurgical (development of a technique for performing Norwood's operation in the modification of R. Mi-Sanno with a homograft, in hypoplasia syndrome

of the left heart); cardiological (heart damage in drop infections in children; differential diagnosis of syncopal states, hereditary heart rhythm disorders; assessment of the functional state of the myocardium of primary school children, and neonates depending on birth weight, myocardial remodeling depending on a number of comorbid conditions: diabetes mellitus, arterial hypertension); pulmonological (bronchoscopy in complex examination and treatment of children with lung diseases); gastroenterological (pathomorphology of chronic gastritis in children with juvenile chronic arthritis). The authority and accumulated experience of the department allowed it to become a regional branch of the European Centre for Training of Adolescent Health Professionals EuTEACH (European Training in Effective Adolescent Care and Health). The results of research work are patents and their implementation in practical health care, publications of articles, presentations at scientific and practical conferences in St. Petersburg, other cities of the Russian Federation and abroad.

The Department annually holds conferences with international participation: EuTEACH Summer Schools 'Adolescent Health Protection (2015), Apostolov Readings: "Modern problems of paediatric gastroenterology" (2015–2017), "Hereditary diseases in paediatrics and gastroenterology". Modern methods of diagnostics and personalized therapy' (2018), Russian Congress with international participation "Molecular bases of clinical medicine — possible and real" (2016, 2018), "Traditions and achievements of Russian paediatrics" (2015–2024), scientific-practical international conference "Modern biotechnologies for science and practice" (2019), scientific conferences of SSS (2014–2024 annually), schools-seminars for paediatricians with clinical cases.

Over the last decade, the department team has published 14 monographs and chapters of guidelines: National manual "Paediatrics" in two volumes, manuals "Paediatric Cardiology", "Paediatric Gastroenterology", "Adolescent Medicine", "International Handbook on Adolescent Health and Development", textbooks "Propaedeutics of Paediatric Diseases" and "Paediatric Diseases" in two volumes, "Consultant in 5 minutes", Basic Paediatrics (2023), Norms for the assessment of physical development of children and adolescents of the Russian Federation: A textbook for doctors: in two parts (2022), Nelson's Paediatrics in four volumes (2024).

16 dissertations for the degree of PhD in Medical Sciences and 1 for the degree of Doctor of Medical Sciences were successfully defended under the guidance of the professors of the department. Since 2011, 14 patents have been confirmed.

Prospects of development of the department are connected with preservation of traditions, integration of achievements in science and practice and constant development of scientific directions in paediatrics. The establishment of the paediatric faculty is associated with the development of curricula for theoretical and practical training of junior students, improvement of distance learning methods for all programs: from specialist courses to the training of doctors in advanced training and professional training programs. Practical orientation of all department staff is especially valuable (Fig. 6), each member of the department is a highly professional clinician, who makes daily complex decisions related not only to health, but also to patient's lives. This fact determines the possibility of organizing and conducting educational processes at the highest level.

The history of the Department of Paediatrics and Paediatric Cardiology of the St. Petersburg State Medical University named after I.I. Mechnikov is an integral scientific paediatric school based on high standards in medicine and education focused on the well-being of children. The traditions of the past continue to inspire the modern team for new achievements and success.

ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 14.05.2024 г.

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

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

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В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

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

Размещение публикаций возможно только после получения положительной рецензии.

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

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ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА И ИЗМЕНЕНИЯ ЕГО УСЛОВИЙ

Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Children's Medicine of the North-West» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т. е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

ОФОРМЛЕНИЕ РУКОПИСИ

Редакция журнала приветствует полностью двуязычные статьи.

Статья должна иметь **(НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ)**:

1. **Заглавие** (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.

2. **Сведения об авторах** (публикуются). Для каждого автора указываются: фамилия, имя и отчество, ученая степень, место работы, почтовый адрес места работы, **e-mail, ORCID, SPIN-код.** Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях или по системе BGN (Board of Geographic Names), см. сайт http://www.translit.ru.

3. **Резюме (Abstrsct)** (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Children's Medicine of the North-West» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

Рекомендуемая структура резюме: введение (Introduction), цели и задачи (Purposes and tasks), материалы и методы (Materials and methods), результаты (Results), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. Объем текста авторского резюме определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах 200–250 слов (1500–2000 знаков).

4. **Ключевые слова** (Keywords) от 3 до 10 ключевых слов или словосочетаний, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «ключевые слова». Предпочтительно использовать ключевые словосочетания из 2–4 слов, наиболее точно отражающих тему статьи. Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются запятой.

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

6. **Сокращений,** кроме общеупотребительных, **следует избегать.** Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

7. При представлении рукописи в Журнал Авторы несут ответственность за раскрытие своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

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

8. **Литература** (References). Список литературы должен представлять полное библиографическое описание цитируемых работ в соответствии с NLM (National Library of Medicine) Author A.A., Author B.B., Author C.C. Title of article. Title of Journal. 2021;10(2):49–53. Фамилии и инициалы авторов в пристатейном списке приводятся **в порядке упоминания** (1, 2, 3 и т.д.). В описании указываются ВСЕ авторы публикации. Библиографические ссылки в тексте статьи даются цифрой в квадратных скобках. Ссылки на неопубликованные работы не допускаются.

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Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. … канд. психол. наук. СПб.; 2021.

Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: https://rosstat.gov.ru/folder/12781 (дата обращения: 23.10.2023).

Для всех статей необходимо указывать индекс DOI в конце библиографического описания, а также EDN при его наличии.

Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547–52 EDN: YRAEPZ.

Voropaeva E.E., Khaidukova Yu.V., Kazachkova E.A., et al. Perinatal outcomes and morphological examination of placentas in pregnant women with critical lung lesions in new COVID-19 coronavirus infection. Ural Medical Journal. 2023;22(2):109–121. DOI: 10.52420/2071–5943–2023–22–2-109–121 EDN: CXRCMN. (In Russian).

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

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Ellingsen AE, Wilhelmsen I. Sykdomsangst blant medisinog jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести

официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

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Примеры перевода русскоязычных источников литературы для англоязычного блока статьи.

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219–0678.2019.35.1.056–065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract. report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma "Mat' i ditya". Part 1: Moscow; 2000; 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание Интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: https://rosstat.gov.ru/folder/12781 (accessed: 10/23/2023). (In Russian).

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's ac-

counts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/47/ (accessed: 11.09.2013).

Пример списка литературы (References):

ЛИТЕРАТУРА

1. Криворученко В.К. Жестокое обращение с ребенком. Проявление и меры предотвращения. Информационный гуманитарный портал Знание. Понимание. Умение. 2012; 3. Доступен по: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (дата обращения: 27.12.2023).

2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231–239. DOI: 10.3238/arztebl.2010.0231.

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1. Krivoruchenko V.K. Child abuse. Manifestation and prevention measures. Informatsionnyy gumanitarnyy portal Znaniye. Ponimaniye. Umeniye. 2012; 3. Available from: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (accessed: 27.12.2023) (In Russian).

2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231–239. DOI: 10.3238/arztebl.2010.0231.

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

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

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

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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.

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