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MEDICAL AND SOCIAL ASPECTS OF CHILD ABUSE

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Abstract. The article provides a review of the literature on the problem of child abuse, which until recently was hushed up in our country and did not have the same relevance as it does now. By decree of the President of the Russian Federation V.V. Putin, the period is 2018 to 2027. declared the decade of childhood in Russia, one of Russia's national priorities is to ensure a prosperous and protected childhood. Identification and prevention of various forms of childhood ill-being and child abuse is an important medical and social problem. To effectively prevent and identify child abuse, as well as its impact on the psycho-emotional state, social adaptation, childhood morbidity and mortality, injuries and disabilities, an interdisciplinary approach is required with the involvement of socio-legal employees, teachers and doctors of all specialties.

Key words: *child abuse; neglect; torture; sexual abuse; physical abuse; psychological abuse; emotional abuse; educational neglect; medical neglect; harm to health; forensic examination.*

МЕДИКО-СОЦИАЛЬНЫЕ АСПЕКТЫ ЖЕСТОКОГО ОБРАЩЕНИЯ С ДЕТЬМИ

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Резюме. В статье представлен обзор литературы по проблеме жестокого обращения с детьми, которая до недавнего времени в нашей стране замалчивалась и не имела такой актуальности, как сейчас. Указом Президента РФ В.В. Путина период с 2018 по 2027 годы объявлен десятилетием детства в России; одним из национальных приоритетов страны является обеспечение благополучного и защищенного детства. Выявление и профилактика различных форм детского неблагополучия и жестокого обращения с детьми — важная медико-социальная проблема. Для эффективного предупреждения и выявления жестокого обращения с детьми, а также его влияния на психоэмоциональное состояние, социальную адаптацию, детскую заболеваемость и смертность, травматизм и инвалидизацию, необходим междисциплинарный подход с привлечением социально-правовых сотрудников, педагогов и врачей всех специальностей.

Ключевые слова: *жестокое обращение с детьми; пренебрежение; запущенность; истязание; сексуальное насилие; физическое насилие; психологическое насилие; эмоциональное насилие; образовательное пренебрежение; медицинское пренебрежение; вред здоровью; судебно-медицинская экспертиза.*

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The problem of cruelty to children is relevant throughout the world [1]. Issues relating to child malfortune are also being considered in Russia; they have to be resolved in the general structure of government tasks concerning demographic policy, the quality of life, creation of necessary and sufficient conditions in order to develop a full-fledged personality. In the last decade, ensuring prosperous and safe childhood has become one of Russia's national priorities. As a way to reduce child mortality, improve the health of the child population and improve the quality of medical care for children, different campaigns are being carried out. May 29, 2017 President of the Russian Federation V.V. Putin signed a decree declaring 2018–2027 the Decade of Childhood in Russia. The purpose of the Decree is "to improve state policy in the field of child protection, taking into account the results achieved during the implementation of the National Strategy of Action for Children in 2012–2017". The Russian Federation Government developed an Action Plan for 2020. One of its main directions was to create the system in order to protect and ensure children's rights and interests [2].

Nevertheless, in recent years Russia has seen an increase in the number of crimes committed against the family and minors. Annual state reports "On the Situation of Children in the Russian Federation" provide statistical data characterizing the critical situation of children in modern Russia. Thus, the number of children who have been victims of crime has increased for the last 3 years by 4.5% (2021 — 112,387; 2020 — 94,881; 2019 — 107,571). The number of crimes against sexual inviolability and sexual freedom of minors (2021 — 16,887; 2020 — 15,822; 2019 — 14,755) and children (2021 — 12,251; 2020 — 11,287; 2019 — 11,462) has increased annually.

The State report On the Situation of Children and Families with Children in the Russian Federation for 2021 notes that in 2021, 1,342 criminal cases were initiated in respect of parents or other legal representatives who do not fulfill their obligations to bring up minors and who permit cruel treatment of children, on the grounds of crimes under article 156 of the Criminal Code of the Russian Federation (2020 — 1,288; 2019 — 1,491).

Analysis of the situation regarging protection of minors from criminal encroachments shows that more than half of crimes against children are committed by parents or other legal representatives (2021 — 57.5%; 2020 — 52.6%; 2019 — 55.1%). As total number of crimes against children increased (2021 — 59,426; 2020 — 47,514; 2019 — 54,720), the number of especially serious (2021 — 1,345; 2020 — 956; 2019 — 957) and serious (2021 — 477; 2020 — 434; 2019 — 421) crimes, medium (2021 — 313; 2020 — 274; 2019 — 327) and minor crimes (2021 — 57,291; 2020 — 45,850; 2019 — 53,015) rose as well. The surveys indicated 14.5 thousand facts of inadequate fulfillment of duties on maintenance and upbringing.

The territorial bodies of the Ministry of Internal Affairs of the Russian Federation proactively sent 557 materials to the guardianship authorities for consideration of the deprivation or restriction of parental rights with regard to parents (other legal representatives) who maliciously evade their childcare obligations.

The 2021 report of the Commissioner for Children's Rights, M.A. Lvova-Belova, states that the number of suicide attempts among minors has increased by almost 13% over the past three years (from 3,253 to 3,675 cases) and the number of repeated attempts by rose 92.5% (from 188 to 362 cases) respectively. According to the Russian Investigative Committee, the number of child suicides increased by 37.4% in 2021 compared to 2020 and amounted to 753 cases. In 2018, the Investigative Committee of the Russian Federation recorded 788 suicides among minors, in 2019 — 737, and in 2020 —548 [3]. Thus, the problem of child neglect and child abuse in Russian society is steadily gaining momentum.

The problems of violence against children in families have been discussed since the early 1990s in Russia, when the government began to establish shelters, social rehabilitation centers, and crisis services. The majority of children entering these institutions had experienced violence or abuse as well as its consequences. These children were not as much beaten (although many were physically punished) as they weren't fed, taken to school, cared for and loved. In this regard, the concept of "violence" is used conventionally in this context. In the Russian language, the term "violence" usually refers to specific actions ("beating", "rape") and does not take into account the variety of actions (or inaction) on the part of adults that harm a child. Situations in which a toddler is left unattended at home or in the street, forced to stand in a corner for hours, regularly humiliated and called an "idiot", stripped and fondled, shown pornographic films, poorly fed and clothed, not

provided with a learning environment, given excessive demands and expectations and then punished for not meeting them — all these situations have many similarities in their consequences, but some of them cannot be called violence in the ordinary sense of the word. They are all "bad", "cruel", "wrong" treatment of a child, which traumatizes and negatively affects the child's development and health.

Such treatment can be both conscious and unconscious, can be connected with external factors and the characteristics of parents or a child, can be determined by parents' actions or, conversely, by his or her inaction (for example, failure to provide safety).

In 1999, a World Health Organization report [4] defined child maltreatment as follows: "Child abuse, or maltreatment, includes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect, negligence, and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power".

The causes of child abuse and maltreatment are partly attributable to numerous ethnic and social conflicts, a sharp decline in social mores, and the loss of the best traditions of family upbringing. The rising number of asocial families, families with low income or below the poverty line, their social isolation, alcoholism and drug addiction of parents contribute to an increase in the level of general aggression and anger in the relationship between parents and children. From these positions, many authors reckon that child maltreatment is a problem of society [5–9].

Studies of parents among whom cases of child abuse were identified, showed that they have the following psychological, behavioral or personal characteristics: low self-esteem, lack of restraint, immaturity, a tendency to dictate, aggressiveness, isolation from family and friends [10–12]. It was noted that child abuse is a much more complex phenomenon than a simple consequence of pathological development of an individual. Many authors identify a number of factors that determine the development of the "child abuse syndrome", such as the relationship between a parent and a child, existing family patterns and problems, stress caused by the socio-economic environment, and, in a broader sense, by social conditions [13–21].

According to J. Bowlby, author of the Attachment theory, an infant must receive enough warmth and tenderness from those who raise him for further normal development. Attachment to a mother or a substitute is a genetically programmed process that ensures infants' survival. The formation of psychological attachment is realized indirectly, through socio-psychological factors, which include: the relationship with the child's father, the desirability of pregnancy, own socio-economic status, the presence of family support, mother's expectations from th child [22].

E.G. Eidemiller, V.V. Yustitskis in their work "Psychology and psychotherapy of the family" characterized types of families, where violence against the child is most common:

- families where physical violence as a way of solving problems, becomes a part of family relations;
- families where the mother or father suffers from alcoholism, which destroys emotional ties between parents and children and consequently removes moral and ethical prohibitions on violence against children, including sexual violence;
- families where marital relations are broken for various reasons and there is no possibility of satisfying their sexual needs outside the family, which may lead to sexual violence or child molestation;
- socially isolated families, where parents themselves avoid any close relationships with the people around them including relatives;
- dysfunctional families, where a child take child care responsibility for younger ones due to necessity [23].

The role of the family in the development of child maltreatment has also been studied by other authors [22, 24–27].

Although, according to some researchers, sexual and psychological violence is equally common in both affluent and poor families, children more often serve as a target of negative emotions resulting in various forms of violence in families with low income [28]. Various manifestations of violence against children are especially noticeable during periods of social and socio-economic change [29]. Traditions and customs adopted in a particular culture can dictate cruelty in child-rearing practices. For example, female circumcision is practiced in some Middle Eastern and Asian countries. It is estimated that about 100–140 million girls and women worldwide have undergone

some form of circumcision, and 2 million are at risk each year because of the procedure (most of these women are from Africa, the Middle East and Asia). Female circumcision can be performed both in younger and older children as well as during adolescence. Deliberate damage to healthy organs for non-medical reasons is condemned by the World Health Organization, the International Confederation of Midwives and the International Federation of Obstetricians and Gynecologists. Female circumcision is regarded as a form of violence against girls and women [30, 31].

In accordance with ICD-10, the "the child maltreatment syndrome" is included in Class XIX, "Injury, poisoning and other certain effects of external causes", with the following subheadings: T.74.0 — Neglect or abandonment; T.74.1 — Physical abuse; T.74.2 — Sexual abuse; T.74.3 — Psychological abuse; T.74.8 — Other symptoms of abuse; T.74.9 — Unspecified abuse syndrome [32].

Most authors highlights four main types of child maltreatment: physical abuse, sexual abuse, psychological or emotional abuse, and neglect of a child's basic needs [14, 22, 33].

Neglect is the failure to provide for a child's basic needs. Neglect can be physical, educational, medical or emotional. According to those countries where detailed statistics on child neglect are kept, this type of maltreatment is the most common and is directly linked to high rates of morbidity and mortality in children [34, 35].

Physical neglect is the most common type of neglect, manifested by failure to meet a child's basic needs for food, shelter, and clothing, unrelated to lack of financial resources. Physical neglect also includes inadequate parental supervision, abandonment, expulsion from home, and abandonment of a runaway child who wants to return home.

Pedagogical neglect includes failure to organize adequate education for the child in secondary school, including failure to enroll the child in school or enabling chronic absenteeism, as well as lack of education for children with special educational needs. We find it necessary to elaborate on an infrequently mentioned but often recently encountered type of neglect — medical neglect.

Medical neglect is the postponement or deprivation of necessary medical care or surgical intervention for conditions that are life-threatening or cause harm to health with varying degrees of severity by persons who are obliged to provide care for the child [37, 38]. Medical neglect should include not only life-threatening situations, but also mild or moderate situations that potentially jeopardize the child's health (e.g., lack of preventive examinations, including dental care). There are several forms of medical neglect:

Postponing seeking medical care (parents overlooking obvious symptoms of a child's serious illness or failing to provide their child with adequate preventive care):

- irregular medical care for chronically ill children (insufficient adherence to treatment: parents do not follow the child's treatment regimen, do not give medications at the exact time and in the full dose, do not follow recommendations on nutrition and storage of medications, do not bring the child to the doctor for regular dispensary monitoring);
- deprivation of medical care (parents consciously refuse to comply with medical recommendations);
- refusal to vaccinate.

There is no single reason why parents do not seek medical help in a timely manner or do not fully comply with the doctor's recommendations or deprive their child of medical care recommended by the doctor. Cases of medical neglect are usually the result of a combination of factors and causes on the part of parents, family, child and society. Medical neglect is most often observed when a child has a severe terminal illness, malformations, or impaired psychomotor or cognitive development. Risk factors for medical neglect are also other situations in the family: single-parent family, large family, low socioeconomic level of the family, family isolation (territorial, social), peculiarities of the parents' personality — the presence of alcohol or drug addiction, mental retardation, social immaturity, depression, mental or psychological disorders, which are characterized by indifference or inability to sympathy [36–38]. Lack of parental awareness, lack of sufficient general knowledge and culture (including hygiene knowledge and health culture), mistrust of doctors and lack of partnership with health professionals play an important role in the occurrence of medical neglect.

Diagnosing medical neglect in children is difficult and always requires convincing evidence. Medical neglect should be considered a situation where medical care is available and has an obvious or proven positive effect on the child's health, but is not used by an initiative of parents (legal

representatives), distinguishing the following criteria:

- failure to seek medical assistance when there is a real or potential risk to the child's health or life;
- refusal of medical assistance (surgery, blood transfusion, organ transplantation);
- neglecting or failing to comply with medical recommendations (non-compliance with dispensary monitoring, taking medication, limiting physical activity);
- ignoring preventive measures (immunizations) in the absence of medical contraindications.

The primary aspect of preventing medical neglect is health education work with parents (legal representatives), in which it must be evidently explained that treatment (prevention) offers more advantages than the natural course of the disease without medical intervention, refusal of treatment will aggravate the harm to the child's health, and prevention of infectious diseases through vaccination creates not only individual but also collective immunity, which is a barrier to the spread of infection and the emergence of a disease.

National standards of care and standardized clinical protocols play an important role in proving that a medical intervention is necessary (has an obvious or proven effect). Local clinical protocols should determine the availability of medical care. An urgent medical task is to develop clear criteria/indicators to determine which amount of care provided by parents should be considered as inadequate in case a child suffers from specific diseases.

Emotional neglect, which, like emotional abuse, is difficult to prove, includes inattention to the child's need for love, denial or failure to provide necessary psychological support, chronic or extreme spousal abuse in the presence of the child (e.g., beating a mother, murder).

Physical abuse is trauma or injury deliberately inflicted on a child by parents, legal representatives or other adults, resulting in physical and/or psychological developmental delays and health problems [39]. Physical violence can range from disciplinary actions with minor superficial injuries (bruises, abrasions) to fatal injuries, it might be single or systematic. Physical abuse includes punishment that is inappropriate for the child's age, physical development, health, intellectual or emotional state. Physical abuse includes: beating a child (hitting the body or head with fists or kicks), cauterizing, hitting the buttocks with hands, backhanding, slapping, pulling out or cutting out wisps of hair, sharp and intense shaking, dousing with cold water, painful pinching, twisting an ear, requiring a child to kneel or stand in an uncomfortable position for long periods of time, forcing a child to put hot pepper, salt, baking soda into his or her mouth [4]. Evidence of physical violence, first of all, are injuries of soft tissues. But it should not be forgotten that the injuries may also be accidental, i.e. unintentionally caused. Forensic experts always face the question how a damage was caused, thus, expert practice has accumulated a considerable list of signs that allow to differentiate accidental impact of a damage from an intentional one.

Blood bruises, which are formed by intentional impacts, are multiple, their age is different, they are localized in the area of buttocks, thighs, genitals, cheeks, neck and other parts of the body, their shape and size correspond to characteristics of objects which formed the damage; at the same time, the discrepancy between the parents' story about the time of injury and the objective age of the bruise (objective determination is made by fixing its color) draws attention to itself. Wounds (in particular, from biting with teeth) have an oval shape, uneven bruised edges (cats or dogs leave triangular-shaped wounds after bites, bruises are not common). Fractures also have some peculiarities: a fracture of the acromial end of a clavicle (it is formed if the child's arm is sharply "jerked" upward) is indicative as well as the presence of several fractures in different stages of healing.

Sexual abuse is involvement of a child (with or without his or her consent) in direct or indirect acts of a sexual nature with an adult in order to obtain sexual gratification or benefit, resulting in harm to the child's physical and mental health and behavioral abnormalities that impede further social adaptation [40]. P. Summit proposed the term "accommodation syndrome", which includes five stages, to designate the process of child involvement in sexual activity: Stage 1 — secrecy, Stage 2 — helplessness, Stage 3 — accommodation, Stage 4 — attempted recognition or disclosure, Stage 5 — retreat [41]. The age distribution of sexual assault victims is as follows: about 25% are 0–5 years old, about 35% are 6–11 years old, and 40% are 12–17 years old [42–46].

Forensic examination reveals the following signs (physical indicators of sexual violence): damage to the genital area, anal area in the form of abrasions, lacerations, bruises, pigmentation; defloration; "gaping" of the anus; detection of sexually transmitted diseases, urinary tract infections; pregnancy; urinary and fecal incontinence; psychosomatic diseases and neuropsychiatric disorders [47–49].

Emotional (psychological) violence is a single or chronic mental impact on a child, hostile or indifferent attitude, as well as other behavior of parents or legal representatives, which causes a child's self-esteem disorder, loss of self-confidence, hinders his/her development and socialization [50]. Manifestations of mental violence according to J. Garbary are: ignoring, rejection, threats, including threats with swinging a fist or a heavy object, terrorization, isolation, depravity. This type of violence can be carried out not only in the family, but also in various institutions (so-called institutional violence) [51].

Consequences of abuse. Some authors believe that the result of violence or neglect of children's basic needs can be defined as their traumatization [52]. In this sense, the concept of trauma applied to child maltreatment includes parents' or caretakers' actions resulting in violations of child's psychological, emotional, cognitive and social functioning. According to A.L. Zadarnovsky et al. [53], besides direct physical impact, family violence also contributes to long-term stress (as a damaging factor), causing the formation of persistent health disorders. This fact allows us to conclude that victims of domestic violence with its prolonged existence and damaging effect on the state of health have a group of somatic disorders which have an etiopathogenetic connection with the facts of violence, and that is confirmed by clinical practice. As studies have shown [54, 55], children who have undergone such a demonstrative psychic trauma as abuse in their families, in most cases are characterized by the presence of all symptoms of posttraumatic stress disorder: compulsive reproduction of a traumatic situation, increased physiological excitability, and impaired functioning.

Child abuse and neglect at an early age result in disturbances in main neurobiological systems: the hypothalamic-pituitary-adrenal system (stress response), the amygdala (emotion processing and emotion regulation), the hippocampus (learning and memory processes), the corpus callosum (integration of functions between hemispheres), and the prefrontal cortex (higher cognitive regulatory and executive functions) [56]. The nature of these changes depends on the period of life, i.e. the age of a child. The period of infancy and early childhood is the most vulnerable period for possible severe consequences of maltreatment ranging from impaired brain development and maturation to fatal outcomes. The most common form of physical abuse in early childhood is blows to the head and body, accompanied by head injuries, internal organ damage and fractures; excessive vigorous shaking of limbs or shoulders is also dangerous at this age and can cause hidden intracranial and intraocular bleeding without signs of external injury (battered child syndrome) [57]. The consequences of neglect are also dramatic. Non-compliance with care standards leads to disruption of nutrition and regular sleep, which might be manifested by a significant lag in physical development up to deprivation dwarfism [58]. The consequences of emotional neglect are manifested in behavioral signs of mental retardation: lack of smiling and facial expression, presence of disgust in the gaze, use of self-stimulatory actions, intolerance to changes in the familiar environment, and low activity level [59].

Impaired intellectual and speech development without signs of neurological disorders have been found among preschool and early school-aged children suffering from maltreatment. Cognitive deficiency might be caused by the effects of physical abuse, namely its influence on social information processing abilities; altered results of this process lead to chronic aggressive behavior and a tendency to seek social provocations [60]. In particular, studies of brain electrical potentials in children with psychotraumatic experiences show patterns of neural activation during tasks requiring executive functions similar to the patterns observed in children with attention deficit hyperactivity disorder [61]. The first suicide attempts and self-harm among maltreated children appear between the ages of 7–12 years [62], and children of this age also show increased levels of depression, hopelessness, and low self-esteem. This age period is vulnerable to emotional abuse factors: bullying, terrorizing, and intimidating the child (e.g., constantly belittling the child or destroying a favorite object).

Risks of sexual violence increase with puberty, reaching their highest levels by adolescence. Rates of sexual violence are 1.5–3 times high-

er among girls than among boys [63]. There are immediate and long-term consequences of sexual violence in minors. Near-term consequences include non-traumatic (invasive) and traumatic ones. Non-traumatic consequences are represented by pregnancy (7.7%), sexually transmitted diseases (26.9%), nonspecific colpitis (28%). Traumatic consequences are divided into anatomical and functional ones. Anatomical: most commonly edema (21.9%), lacerations (15.6%), hyperemia (14.8%), abrasions (14%), tears (5.5%), hemorrhages (4.3%), scars (4.4%), hymenal injuries (48.7%), vaginal vestibule injuries (19.5%). Somatic injuries were identified in 20.5% of cases. The percentage of victims with any psychological problems (mainly post-traumatic syndrome, psychosis and depressive reactions) after their sexual abuse ranged from 46.9 to 55.1%. Among the remote consequences, the most frequent were menstrual disorders (11.6%) — gynecological consequences, and vaginismus of central genesis, such as psycho-emotional maladjustment, sexual dysfunction and other disorders. [64]. Sexual abuse also contributes to the manifestation of depressive and schizophrenia-like disorders and leads up to one-third of affected adolescents to commit suicidal acts [65].

The consequences of emotional abuse are psychosomatic diseases (bronchial asthma, dermatitis, etc.) [66, 67].

In adults, childhood abuse causes psychological disorders (helplessness, low self-esteem, guilt, shame), behavioral and emotional disorders (stress disorders, substance abuse disorders, difficulties in close or intimate relationships, dissociative (traumatic) amnesia, dissociative identity disorder, borderline conditions, antisocial personality disorders, somatization and other medical problems, overeating) [68, 69]. The consequences of such violence can be hidden for a long time, and manifest in adulthood as a tendency to repeat adverse experiences and a predisposition to fall into adverse situations (victimization) [70, 71].

Recently, the diagnosis "child abuse syndrome" has been increasingly used in medical documents by Russian pediatric surgeons, traumatologists, and pediatricians. Official statistics on child traumatism and mortality do not fully reflect the total number of children who have suffered from abuse [72, 73]. Neglect of children's needs is "masked" behind a set of other diagnoses: hypotrophy, dermatitis, streptoderma, dehydration, etc. These diagnoses do not reflect the true causes of the identified diseases and, consequently, do not provide grounds for a response from relevant agencies. Thus, cases of deterioration in the health of minors as a result of medical neglect (neglected forms of diseases, disability, etc.) remain in the "invisible zone". Due to regulatory and legal uncertainty in unification of such diagnoses, parents and legal representatives neglecting medical assistance often escape further investigation as such cases are rarely reported by medical professionals [74]. In light of the increased attention to the quality of medical care provided to the population, this gap has negative legal consequences, first of all, for medical workers and medical organizations themselves, as parents (or legal representatives) can file a complaint with the prosecutor's office that medical care was improperly provided.

Violence has long been overlooked as a public health problem because it is an extremely vague and complex phenomenon. What is acceptable and what is unacceptable in human behavior, what is considered harm or damage, depends on the cultural and legal norms that exist in a certain society and is constantly being revised as values and social norms change. Nevertheless, health care institutions (along with educational institutions) are the first line to see the signs of child abuse. They play a critical role in identifying and overcoming the child abuse syndrome. To do so, educators and physicians must be both familiarized with the problem and be aware to take measures in order to stop child abuse and protect children's rights.

Thus, an interdisciplinary approach involving socio-legal staff, educators and physicians of all specialties is necessary to prevent and detect child abuse and its consequences which influence on psycho-emotional state, social adaptation, child morbidity and mortality, traumatism and disability. Attentive attitude to a small patient, improvement of methods for assessing the health status of children as well as a revision of modern anthropometric height-weight and functional indicators in different age groups play a great role not only in therapeutic and diagnostic purposes, but also in the production of forensic medical examinations in cases of child abuse. It is also extremely important to observe examination standards and regulations regarding the description of injuries for further forensic examination as it allows investigative authorities to qualify the act and administer justice.

ADDITIONAL INFORMATION

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

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

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

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RECURRENT RESPIRATORY INFECTIONS IN CHILDREN

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Abstract. The lecture presents the anatomical and physiological prerequisites for the occurrence, etiopathogenetic mechanisms and medical and social risk factors for the formation of recurrent respiratory pathology in children of different ages. The possibilities for the prevention of chronic diseases and rehabilitation measures in children with recurrent respiratory infections are described.

Key words*: children; acute respiratory infections; recurrent respiratory infections; risk factors.*

РЕКУРРЕНТНЫЕ РЕСПИРАТОРНЫЕ ИНФЕКЦИИ У ДЕТЕЙ

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Резюме. В лекции представлены анатомо-физиологические предпосылки возникновения, этиопатогенетические механизмы и медико-социальные факторы риска формирования рекуррентной респираторной патологии у детей разного возраста. Описаны возможности профилактики хронических заболеваний и реабилитационных мероприятий у детей с рекуррентными респираторными инфекциями.

Ключевые слова*: дети; острые респираторные инфекции; рекуррентные респираторные инфекции; факторы риска.*

INTRODUCTION

The widespread of acute respiratory infections (ARIs) is an urgent medical and socio-economic problem. The medical science is extremelly intrested in ARI due to its high incidence rate and risks of complications. ARI invloves all age groups in the epidemic process, as well as causes the most significant economic damage in the structure of all infectious pathology [1, 2]. Recurrent acute respiratory infections in children deserve special attention, as they create significant discomfort for patients' the families and pose serious challenges for physicians. It seems expedient to separate children with reccurent respiratory tract infections into a separate group of dispensary observation in order to develop a set of health-improving measures for reducing morbidity [3]. However, developed rehabilitation programs did not show expected results. The analysis showed that health-improving measures for children with recurrent respiratory tract infections are often insufficiently effective as they miss an individual approach in therapy and prevention [4].

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GENERAL INFORMATION AND TERMINOLOGY

Acute respiratory infections are diseases manifested by catarrhal inflammation of the upper respiratory tract and occurring with fever, runny nose, cough, sore throat, and general impairment of varying severity. In most cases, ARIs are self-limiting diseases that end with complete recovery of a patient [1].

Frequently ill children (FIC) is a group of dispensary observation that includes children susceptible to frequent infections of the upper and lower respiratory tract due to transient, correctable disfunctions of imune systems without persistent organic disorders [3].

In 1986 V.Y. Albitsky and A.A. Baranov [5] proposed to include patients into FIC group if the following criteria are met:

Age	Recurrent RTI during one year
Children under 1 year old	4 times and more
Children from 1 to 3 years old	6 times and more
Children from 4 to 5 years old	5 times and more
Choldren older than 5years old	4 times and more
Chronically ill children — RTI lasts longer than 14 days	

Infection index (II) and resistance index (J) was also proposed as a criterion for inclusion:

- II is defined as the ratio of the sum of all cases of ARI during one year to the age of a child. The II in the group of children with FIC varies from 1.1 to 3.5; among rarely ill peers it ranges from 0.2 to 0.3;
- J is defined as the ratio of the number of all cases of ARI to the number of months of follow-up. Infants under 1 year of age can be referred to FIC group if J is ≥ 0.33; however, according to other authors, it must be at least 0.5 [6].

According to the World Health Organization (WHO) and a number of foreign pediatric schools, healthy toddlers tolerate up to 8 episodes of ARI per year. If the incidence is higher, recurrent respiratory tract infections (RRTIs) are considered. RRTIs are repeated, recurrent upper respiratory tract infections in the absence of any underlying pathologic condition [7, 8]. It is proposed to classify a child into RRTI group if the following criteria are present:

Age	Recurrent RTI during one year
Children under 1 year old	7 times and more
Children from 1 to 3 years old	8 times and more
Children over 3 years old	6 times and more
Recurrent acute otitis media, rhinosinusitis — three episodes within 6 months or four episodes within 12 months	
Recurrent pharyngotonsillitis — six episodes within 12 months	

According to Russian authors, FIC make up 14–18% of the total child population, although there might be higher (up to 50%) rates. Preschoolers amount up to 50% of FIC; younger schoolchildren — 15%; adolescents — 10% [9–11].

In 2021, leading specialists of Italian Medical Associations — pediatricians, pediatric infectious disease specialists, allergists, immunologists, hematologists, oncologists, geneticists and otorhinolaryngologists published the Intercommunity Consensus [12]. The paper is based on the results of 213 clinical studies published on PubMed and Embase electronic resources between 2009 and 2019. The authors estimate that about 25% of infants under 1 year and 6% of children under 6 years suffer from RRTIs. Harmonized criteria for defining patients with RRTIs vary by age and cannot be applied to infants under 1 year.

Age	Frecuency of polytopic respiratory infections
1–3 years	≥ 6 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia, confirmed by clinical criteria and/or radiologically within a year
3–6 years	≥ 5 и5 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia confirmed by clinical criteria and/or radiologically within a year
6–12 yaers	≥ 3 respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) within a year, or
	2 mild cases of pneumonia confirmed by clinical criteria and/or radiologically within a year

Age	Frecuency of polytopic respiratory infections	
Frequency of specific respiratory diseases	> 3 episodes of acute pharyngotonsillitis within a year	
	> 3 episodes of acute otitis media in 6 months and > 4 within a year	
	≥ 2 2 episodes of severe pneumonia confirmed by clinical criteria and/or radiographically within a year	
	> 4 episodes of acute sinusitis (probably bacterial) within a year	
Pneumonia severity indicators	Mild and moderate-severe : temperature < 38.5 °C; • respiratory rate < 50 breaths/ min • light respiratory distress; • no vomiting	Severe: • temperature > 38,5 °C; • respiratory rate > 50 breaths/ min; • severe respiratory distress; • tension of the nose wings; • cyanosis; • grunting; • signs of dehydration; • tachycardia; • capillary refill time > 2

The consensus authors emphasize that RRTI is a diagnosis of exclusion of other chronic conditions such as genetic disorders, cystic fibrosis and CFTR-pathies, primary immunodeficiencies, malformations of the cardiac and respiratory systems, neuromuscular disorders, etc. The Commission also prepared first, second and third level research designs recommended on the basis of clinical and anamnestic picture and practical algorithm.

PREREQUISITES FOR THE RECURRENT RESPIRATORY PATHOLOGY

Numerous factors of various genesis may influence on RRTI formation [13, 14]. The majority of authors mention following most common exogenous factors:

- low level of hygiene and sanitary culture in the family;
- low level of material well-being and unfavorable social and living conditions;
- early socialization of the child (attendance of preschool institutions, mass events, developmental activities, etc.);
- unfavorable environmental conditions (extreme climatic factors, air pollution, passive smoking, etc.);
- irrational use of medicines (antipyretic drugs, antibiotics, etc.);
- malnutrition (early formula feeding, failure to introduce complementary foods at the right time, restrictive diets, etc.)..

Endogenous unfavorable factors include:

- unfavorable ante-, intra- and early postnatal periods (prematurity, morphofunctional immaturity, perinatal pathology, etc.);
- background conditions (rickets, iron deficiency anemia, lymphatic-hypoplastic type of constitution, hyperplasia of lymphoid organs, etc.);
- aggravated family history of allergic pathology;
- deficiency of vitamins (A, D, E, C, etc.), micronutrientst (iron, iodine, selenium, zinc, etc.), polyunsaturated fatty acids;
- malabsorption syndrome;
- disorders of the microbiocenosis.

Morphological features of respiratory tarct organs deserve special attention among other endogenous factors. They intensively grow and differentiate during the first years of life. By the age of 7 years, the formation of respiratory tarct organs ends, and thereafter there is only an increase in their size [13, 14].

Morphologic structure of the respiratory tract organs in young children have following peculiarities:

- thin, easy-to-remove mucous membrane;
- underdeveloped mucus-producing glands;
- reduced production of immunoglobulin A and surfactant;
- capillary-rich submucosa layer, consisting mainly of loose fiber;
- soft, pliable cartilaginous framework of the lower respiratory tract;
- insufficient amount of elastic tissue in the airways and parenchyma.

Most frequently RRTI in children develops due physiologic immaturity of their immune system. The development of the immune system continues throughout childhood. During active growth and development, "critical" periods may be distinguished, which are characterized by high risks of inadequate or paradoxical reactions of the immune system when interacting with antigens [15, 16].

The first critical period lasts from the moment of birth to the end of the first month (the neonatal period). The immune system of a newborn is suppressed, although passive immunity is provided by maternal antibodies; the phagocytosis system has not been developed yet. Newborns show

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weak resistance to opportunistic, Gram-negative flora, so they have a tendency to generalization of microbial-inflammatory processes, and high sensitivity to viral infections.

The second critical period (4–6th month of life) is characterized by the loss of passive immunity due to catabolism of maternal antibodies. The primary immune response after a penetrated infection develops with the help of IgM antubodies and leaves no immunological memory. The same type of immune response develops after vaccination, and only revaccination forms a secondary immune response with the production of IgG antibodies. Later accumulation of secretory IgA leads to insufficient local defense of mucous membranes. Incompleteness of local immunity system is manifested by repeated ARI, intestinal dysbiosis, skin diseases. Such children are highly susceptible to parainfluenza viruses, respiratory syncytial viruses, rotaviruses and adenoviruses. Many hereditary diseases, including primary immunodeficiencies, make their debut. The incidence of food allergies increases dramatically.

The third critical period (2nd year of life) coincides with a significant expansion of child's contacts with the outside world. An incomplete primary immune response to many antigens persists: IgM synthesis predominates, and IgG synthesis suffers from insufficient production of one of the most important subclasses — G2 (antibacterial defense). The system of local immunity remains imperfect due to low levels of secretory IgA. Many primary immunodeficiencies, autoimmune and immunocomplex diseases are manifested for the first time; high sensitivity of children to recurrent viral and microbial-inflammatory diseases of respiratory and otorhinolaryngological organs remains. Manifestations of food allergy gradually weaken.

A characteristic feature of the fourth critical period (6th–7th years of life) is that the average concentration of IgG and IgM in the blood is close to the level of adults; the level of IgA is still lower, which is associated with insufficient local protection of mucous membranes. The content of IgE in blood plasma reaches the maximum level compared to other age periods, which is obviously associated with the high prevalence of parasitic infections — giardiasis, helminthiasis. High level of IgE and low level of IgA is a risk factor for the formation of many chronic diseases of polygenic nature, including allergic diseases. Sensitivity to infectious diseases remains high as well.

The fifth critical period is adolescence (12–15 y. o.); it takes place during active hormonal cahnges. Pubertal growth spurt is combined with a decrease in the volume of lymphoid organs, and the beginning of the secretion of sex hormones (including androgens) is the cause of suppression of cellular mechanisms of immunity; the content of IgE decreases. There is a high sensitivity to viral infections, mycobacterium tuberculosis.

ETIOPATHOGENETIC MECHANISMS OF RECURRENT RESPIRATORY PATHOLOGY

Up to 90% of ARI cases are caused by RNA- and DNA-containing viruses (more than 300 species), but the etiologic structure of pathogens is inconstant and can change even during one epidemic season. 55–60% cases of ARIs remain unidentified. Studies doveted to ARI etiology determined following agents: rhinoviruses (30–50%), coronaviruses (10–15%), influenza pathogens (5–15%) which privailed, and entero-, adeno-, respiratory syncytial and parainfluenza viruses which were detected less frequently (from 2 to 5% in each group) [3, 16–18].

Herpes-virus infections play a major role in the etiology of RRTIs. Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus type VI predominate. Due to the complex strategy of antagonizing and eluding the host immune system, it becomes possible for herpetic viruses to remain in the human body for a long period of time. Herpes simplex virus is a weak inducer of interferon (IFN), so inactivation of viral DNA inside cells does not occur and the virus persists in the cell for a long time. CMV causes destruction of macrophages, sharply suppresses the activity of killer cells, inhibits IFN production and persists in leukocytes and phagocytes for a long time, causing immunodeficient states. The EBV genome is encapsulated in a nucleocapsid, which is covered with the glycoprotein tagument gp350, which is a receptor interaction factor. The virus penetrates into B-lymphocytes through these receptors. EBV is also able to evade immune surveillance during acute infection and reactivation, resulting in viral persistence. In addition, the immunosuppressive effect of EBV contributes to activation of secondary flora, involving the digestive system and nasopharynx in the pathological process. Herpes viruses and adenoviruses persist in 20–30% of children with RRTI during the period of clinical recovery [19, 20].

In recent years, new subtypes of coronavirus (SARS-CoV, HCoV-NKU1, HCoV-NL63, MERS-CoV, SARS-CoV-2) have taken a special place among severe infections with respiratory tract involvement. Severe epidemics of coronavirus infection in 2002 and 2012, and the pandemic of 2019 have placed them on the leading position among all infections with respiratory system involvement [12].

The current etiology of acute respiratory infections often includes several pathogens, namely mix infections (10 to 70%) of respiratory and herpes viruses, followed by bacterial infection. Bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, etc.), chlamydia (*Chlamydia psittaci*, *Chlamydia pneumoniae*) and mycoplasmas (*Micoplasma pneumoniae*, *Micoplasma hominis*) can also be causative agents of ARI. In children aged 3–6 years, associations with streptococcal (16%), mycoplasma (10%) and chlamydia (4%) infections were noted, the course of which is accompanied by pathologic proliferation of lymphoid tissue (in 84%) and abundant growth of opportunistic bacterial pathogens in half of the patients. In 5–10% of cases there is a development of bacterial or viral-bacterial respiratory infections due to changes in the microbiota of the respiratory tract, impaired mucosal defense (mucociliary clearance, MALT) and superinfection with bacterial pathogens [21, 22].

The organism responds to an ARI pathogen with complex defense-adaptive reactions aimed at limiting its reproduction and subsequent elimination, and finally — at complete restoration of resulting structural and functional disorders. Repeated attacks of viruses and bacteria lead to stress, further exhaustion of the immune system, disorders of compensatory-adaptation mechanisms and reduction of immunity resistance, which contributes to the chronicization of the process. Thus, the developped immunologic insufficiency is a pathologic background that forms a group of children with RRTI [1, 10, 11].

Children with RRTIs have increased susceptibility to pathogens due to a shift of the immune response towards the Th2-type, simultaneously local immunity of respiratory mucous membranes is suppressed as evidenced by lower level of IgA in saliva. Spontaneous hyperproduction of proinflammatory interleukins (IL-2, IL-4), including interleukins involved in inflammation chronization (IL-6 and IL-8), is accompanied by an increase in their concentrations in serum, a deficiency of immunoglobulins, a decrease in cellular cytotoxicity (a decrease in the number of activated CD8DR + cells), as well as an increase in the number of cells expressing apoptosis-inducing receptors. In addition, the overwhelming majority of children with RRTI show abnormalities in their interferon system. It was found that an adequate content of IFN in serum is accompamnied by a decrease in induced production of alpha- and gamma-interferons, which reflects the insufficiency of reserve capabilities. Children with RRTI also have dysfunction in the phagocytosis system, characterized by lower levels of phagocytosing neutrophils and cells expressing adhesion molecules (CD 11b), which largely explains their high susceptibility to reccurent respiratory infections and propensity to bacterial complications [23, 24].

The epithelial structures of airway mucosa perform one of the main protective functions. Viral infections damage the cilia that covers the nasal and pharyngeal mucosa, forming areas of "baldness". A single exposure to viral agents is reversible, whereas frequent exposures violate regenerative processes of the mucosa which forms a transitional type of epithelium and facilitate further infiltration by phagocytes and lymphocytes. The damaged basal membrane and the lamina propria of the mucosa provoke the release of transforming growth factor β by fibroblasts, which leads to hyperplasia of lymphoid tissue. Some viruses with tropism to lymphoid tissue (adenoviruses, herpes viruses) inhibit the apoptosis of lymphocytes; as a result, there is a marked hypertrophy of tonsils and lymph nodes. Persistent inflammatory process during RRTIs predisposes to the development of secondary bacterial microflora on the nasal and nasopharyngeal mucosa, forming a combined viral-bacterial pathogenic flora, which also causes hypertrophy of lymphoid tissue [25]. The lymphatic pharyngeal Waldeyer's ring perform a barrier function and participate in the formation of local and systemic immunity. Hypertrophy of nasopharyngeal lymphoid organs in children is a response to respiratory antigenic viral-bacterial load and is currently considered as a physiological process of immune system formation in preschool children. However, when the resistance of lymphoid organs is reduced, pathogenic microorganisms are able to persist for a long time, forming bacterial biofilms [1, 16, 26].

Recurrent respiratory infections, especially in early childhood (before the beginning of active socialization), require the exclusion of various

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hereditary, congenital or acquired pathologies (cystic fibrosis, malformations of bronchopulmonary and cardiovascular systems, otorhinolaryngological organs, gastroesophageal reflux disease, primary immunodeficiencies, etc.) [10, 27].

The conducted examinations revealed that children with RRTIs did not have persistent immunologic changes, however primary immunodeficiencies were verified in 74% of patients with a combination of recurrent viral and recurrent bacterial infections . In most cases, there were non-critical (small) B-cell defects of the immune system (selective IgA deficiency, IgG subclass deficiency, selective antibody formation defect, transient lower levels of immunoglobulins in children). In isolated cases such severe primary immunodeficiency conditions as agammaglobulinemia, hyper IgM syndrome have been detected in children with RRTIs [10, 18]. It was also shown that 40% of patients with isolated recurrent viral infections and 23% of children with a combination of recurrent viral and bacterial infections had bronchial asthma under the mask of RRTI [28]. It should be taken into account that children with RRTIs often have anxiety and general emotional tension, which cause overstrain of the body's psychophysiological systems, the early signs of which manifest in the form of psychosomatic syndromes, including decreased reactivity and increased frequency of illness [6].

POSSIBILITIES OF REHABILITATION FOR CHILDREN WITH RECURRENT RESPIRATORY PATHOLOGY

When treating a patient with RRTI, it is necessary to detail a family history, identify features of intrauterine and early postnatal development, clinical manifestations of diseases, epidemiological and social conditions, which allows to choose the right vector searching for the provoking factors [29].

Rehabilitation of patients with RRTI should include:

- optimal daily and nutritional regimen;
- a full age-appropriate diet;
- regular cold exposure trainings and physical exercises;
- sufficient stay in the fresh air;
- normalization of psychological and social conditions;
- individualized drug therapy,
- scheduled vaccination and non-specific immunological prophylaxis.

Specific immunization helps to reduce the risk of frequent and/or severe diseases in toddlers and preschool children. Vaccination against influenza and the most significant bacterial infections (Pneumococcus and Haemophilus influenzae type B) has shown high effectiveness in reducing the incidence in children [30].

The data accumulated indicates that the colonization of host biotopes by microflora represents a complex ecosystem of metabolic homeostasis and immune tolerance in humans. There is no doubt about an obvious relationship between health status and a gut microbiota, as it plays a crucial role in maintaining metabolic and immunobiologic functions and homeostasis of the organism as a whole [31]. Topical application of antiseptics and local or systemic antibiotic therapy negatively affect the microbiome of children with RRTIs, as it disrupts the qualitative composition and diversity of the child's intestinal microbiota for a long time [32]. It is recommended to prescribe patients with RRTIs:

- probiotics (eubiotics) — live microorganisms, their use in the required amount has a therapeutic and preventive effect; the basic mechanisms of interaction between probiotic bacteria and a host immune system are currently considered in the context of influenting on the balance of Th1/Th2/Th17/Treg-subpopulations. The interaction of ligand-receptor systems are also considered as it provides immune tolerance and anti-infective response of the macroorganism;
- prebiotics, which selectively stimulate the growth of symbiotic microorganisms in the large intestine;
- synbiotics (a combined drug containing several strains of obligate microflora, vitamins, lysozyme, complex multivalent immunoglobulins).

It is recommended to prescribe patients with RRTI immunostimulating agents — drugs that enhance immune response in conditions of weakened immune system [9, 15, 33]. Following drugs are more often used in pediatric practice:

- bacterial lysates;
- herbal preparations;
- interferons;
- inducers of interferon production.

Since there is no vaccination against the majority of ARI pathogens, bacterial lysates (a mixture of antigens of various inactivated bacteria that are the most common ARI pathogens) have been pro-

posed for the prevention of upper respiratory tract diseases. Bacterial lysates have a dual purpose: specific (forming a selective immune response against specific pathogens) and nonspecific (immunostimulatory — activation of key mechanisms of innate and adaptive immunity). Bacterial lysates can be prescribed both in the acute period and for prevention. In the acute period of respiratory infections, it is more effective to prescribe bacterial lysates in combination with appropriate etiotropic therapy [34]. The most well-known bacterial lysate preparations on Russian drug market are IRS-19, Ismigen®, Imudon, OM-85 (Broncho-Munal, Broncho-Vaxom).

Herbal preparations (ginseng, eleutherococcus, thyme, echinacea, honey, rhodiola rosea, milk thistle, chicory, ginger root, birch buds, etc.) contain natural immunomodulators. They should be recommended for use in pediatric practice with a certain degree of caution, since these drugs may cause allergic reactions, especially in sensitized children with RRTI [35].

The modern program of RRTI prevention and treatment of FIC may include pathogenetically justified therapeutic measures with immunotropic effects. Preparations containing interferon α2b (Viferon®, Kipferon®, Grippferon), prevent the attachment and multiplication of pathogens on the airway mucosa as it suppresses viral nucleic acid replication and, at the same time, increases the formation of IgA-antibodies. Moreover, phagocytic activity of macrophages rise along with specific cytotoxicity to target cells of lymphocytes [36].

The use of interferon production inducers is promising concerning RRTI prevention. Interferon production inducers include heterogeneous natural and synthetic compounds with high and low molecular weight united by their ability to activate the production of α-, β- and γ-classes of endogenous IFNs. At the same time, their synthesis is under control of interleukins and repressor proteins and does not reach the level that can have a damaging effect on the body. Moreover, each inducer stimulates IFN synthesis in certain cells that have appropriate receptors [9, 13, 15]. IFN inducers with immunotherapeutic effect include natural low molecular weight polyphenols — gossypol derivatives (megasin, kagocel, savraz, rogasin, gosalidone), and polymers — double-helical RNA (larifan, ridostin). The group of synthetic compounds includes fluorenones and acridanones (amyxin, cycloferon, neovir), and polymers (semidan, ampligen, polyagucil).

A certain tactic of RRTI treatment has developed, which consists in the sequential use of drugs with antiviral activity, IFN and IFN inducers. Drugs capable of inhibiting viral replication should be prescribed during the acute period of viral infections. After acute symptoms and viremia have gone (a subacute period or a recovery period) it is advisable to use IFN inducers in combination with recombinant IFNs to stimulate the processes of immune activation [36].

In a number of cases, the effectiveness of such recovery measures will be insufficient if RRTIs are associated with primary immunodeficiencies, cytopenic conditions, allergies and gastropathology, lack of micronutrients, etc., since special therapy is required in these cases [10, 37].

Clinical and diagnostic examination of patients with RRI should include:

- examination for latent allergies;
- examination for opportunistic infections (herpes viruses);
- examination of interferon status;
- examination of local cytokine status.

The minimum examination complex for children with RRTI should include consultations of otorhinolaryngologists, allergologists, gastroenterologists.

PREVENTIVE HEALTH CHECK-UPS FOR CHILDREN WITH RECURRENT RESPIRATORY PATHOLOGY

Children with recurrent respiratory diseases require a paediatric check-up in health group II (Russian system of classification according to child's health grounds). Accordingly, a prevention program is developed for such kids:

- after recovering from ARI, the child is exempted from physical education lessons for 10 days, then a physical education class with reduced exercise load is recommended;
- a pediatrician examines the child four times a year;
- examination by an otorhinolaryngologist and a dentist — 2 times a year, other specialists — as indicated;
- clinical blood tests and common urine tests — 2 times a year;
- a biochemical blood test and an immunogram — as indicated.

A child is removed from the regular medical check-up list when the frequency of ARIs at the age of up to 3 years is up to 4 times; 3–5 years — up to 3 times; 5–7 years — up to 3 times in a year

and the duration of one episode of illness decreases to 8 days or less [35].

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INFANTILE COLIC

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Abstract. The lecture is devoted to the current problem of pediatrics — infant colic. They are in the light of the recommendations of the Rome criteria, reflecting the opinion of experts — pediatricians, gastroenterologists, allergists. The key to diagnosing infant colic is to exclude organic pathology ("red flags"), which accounts for no more than 5%. The article discusses modern ideas about the pathogenetic mechanisms of infant colic and modern principles of their correction based on these data. Correction of infant colic includes psychological support for the family, continued breastfeeding and the use of probiotics.

Key words: *infant colic; "red flags"; Rome IV criteria; probiotics.*

МЛАДЕНЧЕСКИЕ КОЛИКИ

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Резюме. Лекция посвящена актуальной проблеме педиатрии — младенческим коликам. Они рассматриваются в свете рекомендаций Римских критериев, отражающих мнение экспертов — педиатров, гастроэнтерологов, аллергологов. Ключевым моментом в постановке диагноза младенческих колик является исключение органической патологии («красные флаги»), которая составляет не более 5%. В статье рассмотрены современные представления о патогенетических механизмах младенческих колик и основанные на этих данных современные принципы их лечения. Терапия младенческих колик включает психологическую поддержку семьи, сохранение грудного вскармливания и применение пробиотиков.

Ключевые слова: *младенческие колики; «красные флаги»; Римские критерии IV; пробиотики.*

The term "colic" (colicos) means "pain in the large intestine". Colic is an attack-like pain in the abdomen accompanied by marked restlessness and crying of an infant in the first months of life [1].

A meta-analysis (2017) included 28 diary studies covering 8690 infants, showed that the average daily duration of crying in infants amounts from 117 to 133 minutes per day in the first 6 weeks of life, and to 68 minutes per day — from 10 to 12 weeks of life [2]. The WhyCry 2G crying analyzer identifies five reasons for infant crying: hunger, boredom, pain, sleep and stress. It is estimated that less than 5% of infants have identifiable medical explanations for their crying [3]. Unreasonable infants's cry began to attract the attention of the medical community since the

1890s. For the first time, an infantile colic (IC) was described by M. Wessell et al. in the 1960s [4]. The criteria proposed by M. Wessell et al. were used to diagnose colic for a long time. The criteria consists of the so-called rule of three: crying for 3 hours a day or more (usually not longer than 1 hour), at least 3 days a week, for 3 consecutive weeks; age from 6 weeks to 3–4 months; a good general condition: children have good weight gain, maintain a positive emotional attitude, good appetite, normal stools; possible infrequent regurgitation; absence of "anxiety symptoms". Clinical practice has shown that it was hard for parents to evaluate periods of crying and anxiety retrospectively, thus the Wessell criteria were considered inappropriate for practical use since they were associated with certain difficulties and diagnostic errors. According to the Rome IV criteria revision committee, the Wessell criteria are random, culturally independent, impractical, and do not reflect the impact of the child's symptoms on the family. For this reason, the new clinical criteria are based on symptoms that have been shown to cause more discomfort for parents. In addition, the Rome IV criteria extended the age of IC diagnosis to 5 months [5]. Thus, for clinical purposes, the diagnostic criteria should include following features: an infant under 5 months old at the beginning and end of symptoms; recurrent and prolonged periods of crying, restlessness, or irritability reported by caregivers, occurring for no apparent reason and that cannot be prevented or managed by caring adults; no evidence of developmental delay, fever, or illness with clinical signs, i.e., "red flags" or "anxiety symptoms" [5]. "Anxiety symptoms" indicate organic diseases manifesting itself in fever, persistent regurgitation including coughing fits, absence of weight gain, mucus and blood in stools, passive abdominal wall tension, refusal to eat, abdominal bloating, signs of atopic dermatitis and persistent constipation.

IC is defined as one of the most common complaints that parents adress to primary care physicians [6, 7]. A recently published systematic review (2020) reported colic incidence rates ranging from 2 to 73% [8]. Symptoms peak around the sixth week of life and cease naturally after 4–6 months of age [9], allowing it to be considered a benign, self-healing condition.

The need to treat this self-healing condition stems from the negative impact of excessive crying on an infant's family. Prolonged infant crying is harmful to sibling-parent relationships [10], is associated with maternal problems such as depression, anxiety, and loss of parental confidence [11, 12], is a frequent cause of early cessation of breastfeeding [13], and can lead to severe infant injury or death due to abuse [14]. A second important argument for the treatment of colic is the presence of its long-term consequences, such as migraine, sleep and behavioral disorders, hyperactivity, decreased intelligence and cognitive disorders, eating disorders, atopic diseases and functional gastrointestinal (GI) diseases [15–18]. Knowledge of IC pathogenesis is necessary for selecting an adequate therapy.

Infantile colic has a multifactorial pathogenesis. Physiologic imbalance in the development of the central nervous system explains the time of IC manifestation. At the age of 2 months, brain systems tolerate changes, as a result reflex mechanisms supervising behavioral responses are replaced by a system of control proceeded by the cerebral cortex. Many authors believe that inconsolable crying, which is noted in infantile colics, is a consequence of transient behavioral response deficits in the first 2 months of life [19, 20]. Complex interactions between behavioral factors (psychological and social) such as postpartum depression, parental anxiety, stressful pregnancy, adverse experiences during delivery, poor parenting skills [24–26], alterations from the endogenous opioid system and neuropeptide regulation [27–31], as well as nutritional factors (hypersensitivity or food allergy, especially allergy to cow's milk proteins) [28, 30], immaturity of gastrointestinal tract (GIT) [21, 24, 32], excessive intestinal gases [21, 24], imbalance of intestinal hormones and impaired intestinal motility [31, 32], changes in the intestinal microbiota [33, 34], disruption of the microbiota-brain axis [35], impaired intestinal permeability and low intensity inflammation [22, 36, 37] are among numerous mechanisms that play a role in the pathogenesis of colic.

The role of the gut microbiota has the greatest evidence base in the colic pathogenesis. Table 1 summarizes studies examining the quantitative and qualitative composition of the microbiota in children with and without IC.

Despite the diversity of results, most researchers indicate a low qualitative diversity of intestinal microbiota in children with colic compared to the microbiota of children without colic during the first 2 weeks of life [39]. Other studies suggest the presence of certain microorganisms in the gut microbiota associated with increased

Table 1. Studies of microbiota composition in children with colic and healthy infants

Таблица 1. Исследования состава микробиоты у детей с коликами и здоровых младенцев

Автор / Author	Метод / Method	Результаты / Results
Savino et al., 2004 [38]	Культуральный / Cultural	Младенцы с коликами имеют более высокие показатели и плотность кишечной палочки и других газообразующих кишечных палочек и более низкие уровни *Lactobacillus* spp. по сравнению со здоровыми младенцами / Colicky infants have higher counts and densities of *E. coli* and other gas-forming coliforms and lower levels of *Lactobacillus* spp. compared to healthy babies
Savino et al., 2009 [39]	Культуральный + ПЦР / Culture + PCR	*Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Enterobacter cloacae*, *E. aerogenes* и *Enterococcus faecalis* были преобладающими видами у младенцев с коликами / *Escherichia coli, Klebsiella pneumoniae, K. oxytoca, Enterobacter cloacae, E. aerogenes* and *Enterococcus faecalis* were the predominant species in colicky infants
Mentula S., 2009 [40]	Культуральный + анализ клеточных жирных кислот, КЦЖК и производства газов / Culture + analysis of cellular fatty acids, SCFAs and gas production	Распространенность индолпродуцирующих колиформ была значительно выше у младенцев с коликами по сравнению с контрольной группой, в то время как многие аэробные роды, присутствующие в контрольной группе, не были обнаружены у младенцев с коликами / The prevalence of indole-producing coliforms was significantly higher in colicky infants compared with controls, while many aerobic labors present in controls were not found in colicky infants
de Weerth C., 2013 [41]	Молекулярные методы / Molecular methods	Colic phenotype was positively correlated with *Serratia, Vibrio* and *Pseudomonas* content / Фенотип колик положительно коррелировал с содержанием *Serratia*, *Vibrio* и *Pseudomonas*
Rhoads J.M., 2018 [42]	Секвенирование ДНК / DNA sequencing	Таксоны, которые в значительной степени связаны с коликами: *Acinetobacter*, *Lactobacillus iners*. Снижение относительного содержания бифидобактерий в среднем в 30 раз / Taxa significantly associated with colic: *Acinetobacter, Lactobacillus iners*. Reduction in the relative content of bifidobacteria by an average of 30 times
Loughman A, et al., 2021 [43]	Секвенирование 16S рРНК / 16S rRNA sequencing	Альфа-разнообразие фекальной микробиоты не имело существенной связи с плачем. Несколько таксонов микробиоты (включая *Bifidobacterium*, *Clostridium*, *Lactobacillus* и *Klebsiella*) связаны с тяжестью колик / Alpha diversity of fecal microbiota was not significantly associated with crying. Several microbiota taxa (including *Bifidobacterium, Clostridium, Lactobacillus*, and *Klebsiella*) are associated with colic severity
Kozhakhmetov S., 2023 [44]	Полное метагеномное секвенирование образцов кала / Whole metagenomic sequencing of stool samples	В группе колик обнаружено относительное изобилие *Bifidobacterium* и обогащение *Bacteroides Clostridiales*, в то время как микробное биоразнообразие в этой группе было обогащено /The colic group revealed a relative abundance of *Bifidobacterium* and an enrichment of *Bacteroides Clostridiales*, while microbial biodiversity was enriched in this group
Новикова В.П., 2023 [37] / Novikova V.P., 2023 [37]	Метод газовой хроматографии-масс-спектрометрии по Г.А. Осипову образцов кала / Method of gas chromatography-mass spectrometry of fecal samples according to G.A. Osipov	В группе колик значимо выше уровень *Acinetobacter* spp, *Nocardia* spp. и *Micromycetes* spp. по сравнению со здоровыми / In the colic group, the level of *Acinetobacter* spp., *Nocardia* spp. and *Micromycetes* spp. was significantly higher compared to healthy people

Note: SCFAs — short-chain fatty acids; PCR — polymerase chain reaction.

Примечание: КЦЖК — короткоцепочечные жирные кислоты; ПЦР — полимеразная цепная реакция.

crying duration in infants up to 3–4 months of age. These microorganisms include the family of gram-negative bacteria (Proteobacteria phylum), among which Escherichia, Klebsiella, and Proteobacteria species were predominant in stool samples of infants with colic [39, 42, 45]. Along with these microorganisms, Serratia, Yersinia, and Vibrio species were found in children with colic at the age of 2–4 weeks of life [42]. Two studies revealed significant differences in the content of *Acinetobacter* spp. [37, 42]. The first pathogenetic mechanism in IC connected with the increased content of Gram-negative opportunistic bacteria is excessive gas production as a result of fermentation of lactose, other carbohydrates and proteins. The second possible mechanism is an inflammatory response in the gut, which is triggered by the lipopolysaccharide complex of the outer envelope of Gram-negative bacteria resulting in increased production of pro-inflammatory cytokines and chemokines. High levels of fecal calprotectin and biomarkers of neutrophil infiltration in infants with colic evidence the above mentioned[22, 36]. Intestinal mucosa is more permeable due to inflammation which result in visceral hypersensitivity with clinical manifestation of IC symptoms. At the same time, Bifidobacterium and Lactobacillus microorganisms have an inverse association with colic symptoms in children during the first 3 months of life [34, 36, 45]. The pathogenetic mechanisms explaining the association of these microorganisms with the reduction of colic symptoms are the positive effects of Lactobacilli and lactic acid bacteria on the epithelial function of the intestinal mucosa, its barrier function and intestinal kinetics. Additionally, specific strains of Bifidobacterium and Lactobacillus have an anti-inflammatory response as they have antagonistic effects against gas-producing bacteria including Escherichia, Klebsiella and Enterobacter strains [46].

Each factor influencing on the formation of the intestinal microbiome (maternal microbiome and health status, mother's use of medications, type of delivery, condition of a child after birth, type of infant feeding, use of antibacterial drugs in a neanatal period) separately has no reliable significance in IC genesis [40, 47–49]. At the same time, it was proven that bacterial colonization was associated with malabsorption of fats and other nutrients due to immaturity of enterohepatic circulation of bile acids and salts [15, 24]. Microbiota produces local gut neurotransmitters (serotonin, gamma-aminobutyric acid, melatonin, histamine, acetylcholine) and coordinates local adaptive responses to stressors through the system of neuroimmunoendocrine hierarchy. In addition, the microbiota can alter brain physiology through the production of a wide range of cytokines, short-chain fatty acids, and increased afferent nerve activity. This the way the microbiota-brain axis works, and correspondingly plays a role in the genesis of IC [35].

Lactose tolerance disorder is a physiologic transient state in 3–4 months old infants, it often causes infantile colic. The literature describes the relationship between the severity of pain in infantile colic and the amount of carbohydrate excretion with feces in both breastfed and formula-fed infants. Data show that 25% of infants develop moderate to severe symptoms of colic dependent on cow's milk protein [50–53].

Mothers' conditions also contribute to predisposition of infantile colic, among them: unfavorable obstetric and gynecological history of the mother, gestosis, hypodynamia during pregnancy; nutritional disorders of the nursing mother (consumption of fatty foods, foods that increase flatulence, excessive amounts of cow's milk and its products); bad habits (smoking, alcohol, drugs); emotional stress in the family. Infants' contributions are prematurity; symptoms of post-hypoxic damage to the central nervous system; infant temperament. Incorrect feeding technique (swallowing air during feeding); force feeding; overfeeding; feeding from two breasts, improper preparation of nutritional formula (excessive or insufficient dilution), lack of proper mother-child interaction in the feeding situation also predispose to the development of infant colic [1].

The classic picture of colic is a dyad — extremelly anxious parents and an infant with a persistent, piercing cry that is audiologically distinct from other infant cries [54]. Cry episodes are associated with hypertension, facial redness, pulling the legs up to an abdomen, and flatulence. Assessment of the infant during an episode of colic may indicate that the infant is in moderate to severe pain according to the FLACC scale (Face, Legs, Activity, Cry, Consolability scale, a measurement used to assess pain for children). [55]. The crying starts and stops abruptly on its own, i.e., the nature of the episodes is paroxysmal [55]. It is very difficult to calm the baby. Typical crying of a baby with colic is presented under the QR code.

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XA circadian rhythm of crying (or "crying curve") with maximum intensity of crying and restlessness in the afternoon is specific for IC. An important characteristic of crying is its age-dependent appearance and dynamics: it appears from the 2nd week of life, peaks at 2–3 months of age with6 then gradually decrease and disappears by 4–5 months of age.

The presence of multifactorial pathogenesis leads to difficulties in therapeutic approaches. There are no international consensus documents, and national guidelines compiled by experts from the standpoint of evidence-based medicine are available only in three countries: the UK, the USA, and Ireland [56, 57]. An analysis of the recommendations of these guidelines is presented in Table 2.

In Russia, infantile colic is described in the National Guidelines for Pediatric Gastroenterology [58] and in the 2022 recommendations of the Society of Pediatric Gastroenterologists, Hepatologists, and Nutritionists on Functional Gastrointestinal Tract Diseases [1, 59].

All domestic and foreign guidelines emphasize the need for an individualized approach to the treatment of IC in close cooperation with patient's parents. It is necessary to reassure parents about the transient and benign nature of infantile colic and favorable outcome, to inspire them with confidence in the absence of severe disease in the child. Changing family habits has positive effects, it might be proposed to create a regime of "feeding — activity — sleep"; maintain a positive relationship "child — mother / family". Timely detection of maternal depression, cruel attitude to the child, counseling parents about psychological problems will avoid unwarranted diagnostic intervention in children, as well as anxiety and insecurity in parents [1, 56–59].

Dietary correction measures are considered to be effective as well6 omong them breastfeeding support, assessment of breastfeeding technique and suckling efficiency. Most experts recommend preserving natural feeding [1, 56–59]. A. Cohen Engler (2012) indicated that exclusively breastfed infants had significantly lower rates of colic episodes and tended to have longer nighttime sleep in comparison with formula-fed infants [60]. The authors of the study measured melatonin levels in breast milk every 2 h during the day and found its significant increase during the night hours. It is now known that the circadian rhythm of melatonin in infants is established by 3–5 months of life, and regression of infantile colic is also noted around this age [30]. It was also found that infants with infantile colic had a statistically significant decrease in the level of melatonin in the blood in the morning hours and later establishment of the circadian rhythm of melatonin compared to the control group. It is possible that infantile colic may be associated with desynchronization of the normal circadian rhythm of melatonin, and breast milk, which contains the highest melatonin levels at night, may compensate a transient circadian rhythm deficiency in infants [23]. In addition, night breast milk probably exerts antispasmodic, antioxidant, anti-inflammatory, and immunoregulatory effects on intestinal wall permeability membrane and infant microbiome development [23, 28, 61].

Currently, there are no united nutritional recommendations for breastfeeding women. According to recommendations of the Rome IV criteria, elimination of cow's milk-based products from the diet of breastfeeding women is recognized as effective only in the presence of allergy to cow's milk protein [62]. In all other cases, a causal relationship between maternal diet and colic has not been proven. A number of studies recommend the use of a hypoallergenic diet (exclusion of cow's milk, eggs, peanuts and other nuts, wheat, soy and fish) and associate it with a reduction of colic symptoms in children [63]. A 2012 systematic review identified 1 randomized controlled trial in infants whose mothers followed a diet with low big eight allergens during one week. Questionnaires noted a reduction in crying by 60 minutes over 48 h, however, mothers did not report a subjective decrease of colic. In addition, only 60% of mothers in this study were able to fully comply with the elimination diet, emphasizing the difficulty in implementing dietary restrictions [29, 63]. Based on the above mentioned, most researchers believe that elimination diets are not recommended for breastfeeding mothers as a cure for infantile colic [1, 56–59].

Table 2. Methods of treating colic from the point of view of evidence-based medicine

Таблица 2. Методы лечения колик с точки зрения доказательной медицины

Рекомендация/предложение / Recommendation/proposal	UK, 2013, 2017 [56] / Великобритания, 2013, 2017 [56]	USA, 2015 [56] / США, 2015 [56]	Ireland, 2014 [57] / Ирландия, 2014 [57]
Клиническая оценка отношений матери и ребенка / Clinical assessment of the mother-child relationship	✓	✓	✓
Информация для родителей, советы, поддержка и уверенность / Parenting information, advice, support and reassurance	✓	✓	✓
Продолжение грудного вскармливания / Continued breastfeeding	✓	✓	
Модификация рациона матери / Modification of the mother's diet	✗	✓	
Смена смеси, если ребенок вскармливается смесью (+), если не выявлена аллергия на молоко) / Changing the formula if the baby is formula-fed (+ if an allergy to milk is not detected)	✗	✓	
Пробиотические добавки (++) младенцам, находящимся только на грудном вскармливании) / Probiotic supplements (++ breastfed-only infants)	✗	✓+	✓
Симетикон / Simethicone	✗	✗	
Травяные добавки (например, фенхель) / Herbal supplements (such as fennel)	✗	✗	
Ингибиторы протонной помпы (например, омепразол, Лосек) / Proton pump inhibitors (eg, omeprazole, Losec)		✗	
Лактаза (например, капли Co-lief) / Lactase (eg Co-lief drops)	✗		
Антихолинергические препараты (включая дицикломин) / Anticholinergic drugs (including dicyclomine)		✗	
Детский массаж / Baby massage			✓
Мануальная терапия (включая манипуляции на позвоночнике и краниальную остеопатию) / Manual therapy (including spinal manipulation and cranial osteopathy)	✗	✗	
Физический контакт (например, удержание, раскачивание) / Physical contact (eg, holding, rocking)	✓		✓
«Белый шум» / «White noise»	✓		
Купание / Bathing	✓		
Обмотка (пеленание) / Winding	✓		
Пеленание / Swaddling		✗	
Акупунктура / Acupuncture		✗	
Режим сна / Sleeping mode			

Note: ✓ — recommended; ✓+ — high level of evidence; ✗ — not recommended; blank — not analyzed.

Примечание: ✓ — рекомендовано; ✓+ — высокий уровень доказательности, ✗ — не рекомендовано; пустая графа — не анализировалось.

According to systematic reviews, formula-fed infants of the first 3 months of life suffering from colic symptoms, are recommended to use partially hydrolyzed whey formulas with added prebiotics (oligosaccharides), formulas with reduced lactose content and fat component [1, 56–59].

Probiotic therapy has the highest level of evident efficacy among other therapeutic strategies in colic treatment [64–67]. Currently, the US Food and Drug Administration (FDA) has given probiotics a GRAS (Generally Recognized As Safe) status, which means: recognized as safe by leading FDA experts [48]. Taking into account the above mentioned pathogenetic mechanisms of the relashionship between intestinal microflora and IC, the correction of intestinal microbiome seems promising in the point of reducing colic symptoms. The efficacy of different strains of Lactobacillus reuteri has been demonstrated in naturally fed infants [23, 24, 66–68]. The factors behind the effects of *L. reuteri* are studied well. These are the ability to form biofilms; the resistance of *L. reuteri* colonies to low pH and bile salts; the ability of *L. reuteri* attach to mucin, intestinal epithelium and intestinal epithelial cells; production of metabolites with antimicrobial and immunomodulatory effects, the most studied of which is reuterin, which inhibits a wide range of microorganisms, mainly Gram-negative bacteria, while the strains of *L. reuteri* show marked resistance to reuterin. Some strains of *L. reuteri*, in addition to reuterin, produce other antimicrobial substances: lactic acid, acetic acid, ethanol, reutericycline. Therefore *L. reuteri* is effective against various bacterial infections of the gastrointestinal tract: *Helicobacter pylori*, *E. coli, Clostridium difficile* and salmonellae. Moreover, *L. reuteri* produces metabolites with antiviral properties which are effective against pneumoviruses, circoviruses, rotaviruses, coxsackie viruses and papillomaviruses. In addition, there are reports that L. reuteri also stops the growth and kills various Candida species; some strains of *L. reuteri* inhibit the production of few pro-inflammatory cytokines, affect immune cells, produce folate and gamma-aminobutyric acid (GABA), which determine its effect on visceral sensitization [69].

It should be noted that the effects of different *L. reuteri* strains are strain specific. The proven effects of some *L. reuteri* strains are summarized in Table 3.

Placebo-controlled and comparative studies demonstrate different results of colic treatment with L. reuteri probiotics, both positive and negative [75]. The data are summarized in Table 4.

In recent years, there has been increased interest in the use of other probiotic strains for the treatment of colic. The data are presented in Table 5.

Table 5 shows that Lactobacillus rhamnosus GG (ATCC 53103), Bifidobacterium animalis subsp. lactis, BB-12 and B. breve CECT7263 strains demonstrated a good therapeutic effect in colic in breastfed and formula-fed children. At the same time, multistrain probiotics have been shown to have synergistic effects that individual strains cannot achieve independently. It is suggested that multistrain probiotics may be effective in the treatment of colic due to their synergistic effects [88]. The data are summarized in Table 6.

Other pharmacologic agents that have been traditionally recommended for the relief of colic symptoms include simethicone, chamomile or fennel-based phytosupplements, other carminative and homeopathic preparations [4, 25, 92]. Most randomized clinical trials indicate low efficacy of these treatments. Concurrently, there is a lack of standardization of some homeopathic remedies consumption, as well as potential risks of undesirable effects. Thus, these remedies do not allow recommending most of them for the correction of infantile colic [21, 25, 56, 57, 93]. In some cases prescribed antispasmodics, proton pump inhibitors, and analgesics [3, 24, 66] have not proven effectiveness as well [56, 57]. Data published on lactase preparations for the treatment of colic is conflicting. There is evidence based on the results of randomized controlled trials (RCTs) showing a decrease in crying time in infants with proven lactose intolerance disorder when using lactase preparations compared to placebo [64]. At the same time, there are other RCTs indicating insufficient or weak effect of lactase preparations for relief of colic symptoms in infants on different types of feeding [65, 81]. It seems reasonable to recommend the use of lactase preparations only in case of proven lactase deficiency for 2 weeks. If there is no effect during this period of time, lactase therapy must be canceled.

It should be noted that a number of manipulations, such as infant massage, physical contact (e.g., holding, rocking an infant), bathing, swaddling and listening to the "white noise" have an evidence base for effectiveness agains colic [56, 57] . The "white noise" is a background sound that contains frequencies of the entire sound range, from 20 to 20,000 Hz, it is similar with the sounds

Table 3. Proven effects of different strains of *L. reuteri*

Таблица 3. Доказанные эффекты различных штаммов *L. reuteri*

Автор / Author	Штамм / Strain	Эффекты / Effects
Garcia Rodenas C.L., 2016 [70]	*L. reuteri* DSM 17938	Снижение количества энтеробактерий и повышение числа бифидобактерий у детей, рожденных путем кесарева сечения, т.е. модулировало развитие кишечной микробиоты / A decrease in the number of enterobacteria and an increase in the number of bifidobacteria in children born by cesarean section, i.e. modulated the development of intestinal microbiota
Savino et al., 2015 [53]	*L. reuteri* DSM 17938	Снижение количества анаэробных грамотрицательных и увеличение количества грамположительных бактерий в кишечной микробиоте, тогда как содержание энтеробактерий и энтерококков в значительной степени снижено / A decrease in the number of anaerobic gram-negative and an increase in the number of gram-positive bacteria in the intestinal microbiota, while the content of enterobacteria and enterococci decreased significantly
Martoni C.J., 2015 [71]	*L. reuteri* NCIMB 30242	Увеличивает соотношение *Firmicutes* и *Bacteroidetes* / Increases the ratio of *Firmicutes* to *Bacteroidetes*
Savino F., 2009 [39]	*L. reuteri* DSM 17938	Увеличение количества лактобацилл и уменьшение *E. coli* в фекальной микробиоте / Increase in the number of lactobacilli and decrease in *E. coli* in the fecal microbiota
Savino et al., 2019 [72]	*L. reuteri* DSM 17938	Снижает восприятие боли двумя путями: через переходный рецепторный потенциал — ваниллоидный канал 1, влияя на калийзависимую активность кальциевых каналов и снижение вызванных капсаицином и растяжением потенциалов действия спинномозговых нервов / Reduces pain perception in two ways: through transient receptor potential — vanilloid channel 1, influencing potassium-dependent calcium channel activity and reducing capsaicin- and stretch-induced action potentials of spinal nerves
Hojsak I., 2019 [73]	*L. reuteri* DSM 17938	Снижение уровня фекального кальпротектина / Decrease in fecal calprotectin levels
Pourmirzaiee M.A., 2020 [74]	*L. reuteri* LR92 (DSM 26866)	Выделяет уксусную кислоту, которая снижает pH *in vivo* и оказывает выраженное антибактериальное действие на многие патогены и реутерин, способный вызвать окислительный стресс у патогенов и эффективно предупреждать развитие воспалительной реакции / Produces acetic acid, which lowers pH *in vivo* and has a pronounced antibacterial effect on many pathogens and reuterin, which can cause oxidative stress in pathogens and effectively prevent the development of an inflammatory response
Новикова В.П., 2023 [37] / Novikova V.P., 2023 [37] /	*L. reuteri* DSM 17938	В группе детей, получавших *L. reuteri*, значимо снижался уровень *Bacillus megaterium*, *Bacteroides fragilis* и *Prevotella ruminicola*. Снижение уровня зонулина / In the group of children receiving *L. reuteri*, the level of *Bacillus megaterium, Bacteroides fragilis and Prevotella ruminicola* decreased significantly. Decreased zonulin levels

Table 4. Results of placebo-controlled and comparative studies of treatment of colic with *L. reuteri* **probiotics**

Таблица 4. Результаты плацебоконтролируемых и сравнительных исследований лечения колик пробиотиками *L. reuteri*

Автор / Author	Штамм / Strain	Эффекты / Effects
Лечение эффективно / Treatment is effective		
Savino F., 2007 [76]	*L. reuteri* ATCC 55730	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Szajewska H. et al., 2013 [77]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика в сравнении с плацебо / Reduction in anxiety and cry duration compared to placebo

Ending of the table 4 / Окончание табл. 4

Автор / Author	Штамм / Strain	Эффекты / Effects
Chau K. et al., 2015 [78]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Mi G.L. et al., 2015 [79]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Tatari M. et al., 2017 [80]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Dryl R., 2018 [81]	*L. reuteri* DSM 17938	Положительный лечебный и профилактический эффект исключительно у детей на грудном вскармливании (21–28 дней) / Positive therapeutic and preventive effect exclusively in breastfed children (21–28 days)
Novikova V.P., 2023 [37] / Новикова В.П., 2023 [37]	*L. reuteri* DSM 17938	Положительный лечебный и профилактический эффект в виде снижения плача менее 1 часа к 10-му дню лечения у детей, независимо от вида вскармливания / Positive therapeutic and preventive effect in the form of reduced crying for less than 1 hour by the 10th day of treatment in children, regardless of the type of feeding
Лечение неэффективно / Treatment is ineffective		
Sung V. et al., 2014 [82]	*L. reuteri* DSM 17938	Нет различий с группой плацебо / No difference with placebo group
Fatheree N.Y. et al., 2017 [83]	*L. reuteri* DSM 17938	При искусственном вскармливании не было получено положительного результата / No positive results were obtained with artificial feeding
Dryl R., 2018 [81]	*L. reuteri* DSM 17938	При искусственном вскармливании не было получено положительного результата / No positive results were obtained with artificial feeding

Table 5. Results of placebo-controlled studies of the treatment of colic with different single-strain probiotics

Таблица 5. Результаты плацебоконтролируемых исследований лечения колик разными моноштаммовыми пробиотиками

Автор / Author	Штамм / Strain	Клинический эффект / Clinical effect	Патогенетический механизм / Pathogenetic mechanism
Savino F. et al., 2020 [45]	*Lactobacillus rhamnosus GG (ATCC 53103)*	Значительное снижение плача / Significant reduction in crying	Наблюдалось значительное увеличение общего количества бактерий в образцах кала (*Lactobacillus* spp.) и значительное снижение уровня кальпротектина / There was a significant increase in total bacterial counts in stool samples (*Lactobacillus* spp.) and a significant decrease in calprotectin levels
Xinias I. et al., 2017 [84]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача, повышение качества жизни семьи / Significant reduction in crying time, improved family quality of life	Не изучался / Not studied
Nocerino R. et al., 2020 [85]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача / Significant reduction in crying time	Достоверное увеличение HBD-2, LL-37, sIgA и бутирата и снижение кальпротектина / Significant increase in HBD-2, LL-37, sIgA and butyrate and decrease in calprotectin

Ending of the table 5 / Окончание табл. 5

Автор / Author	Штамм / Strain	Клинический эффект / Clinical effect	Патогенетический механизм / Pathogenetic mechanism
Chen K. et al., 2021 [86]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача / Significant reduction in crying time	Увеличение sIgA, бутирата в конце 21-дневного вмешательства, увеличение кальпротектина β-дефензина-2 и кателицидина / Increase in sIgA, butyrate at the end of the 21-day intervention, increase in calprotectin β-defensin-2 and cathelicidin
Suanes-Cabello S., 2020 [87]	*B. breve CECT7263*	Большая эффективность в сокращении ежедневного времени плача у детей на грудном и искусственном вскармливании, чем в контроле / Greater effectiveness in reducing daily crying time in breastfed and bottle-fed children than in controls	Ингибирование роста *Enterobacteriaceae* spp., противовоспалительное действие / Inhibition of the growth of *Enterobacteriaceae* spp., anti-inflammatory effect

Table 6. Results of placebo-controlled and comparative studies of the treatment of colic with different multi-strain probiotics

Таблица 6. Результаты плацебоконтролируемых и сравнительных исследований лечения колик разными мультиштаммовыми пробиотиками

Авторы / Authors	Состав пробиотиков / Composition of probiotics	Клиническая эффективность / Clinical effectiveness
Gerasimov et al., 2018 [89]	*L. rhamnosus 19070-2* + *L. reuteri 12246* + фруктоолигосахарид и витамин D_3	Значительная разница в среднем времени плача между пробиотиком и контрольной группой / Significant difference in mean crying time between probiotic and control group
Baldassarre et al., 2018 [90]	*L. paracasei DSM 24733, L. plantarum DSM 24730, L. acidophilus DSM 24735 L. delbrueckii subsp. bulgaricus DSM 24734), B. longum DSM 24736, B. breve DSM 24732 B. infantis DSM 24737) Streptococcus thermophilus DSM 24731*	Статистически значимое снижение количества минут плача в день. Незначительная разница в общем количестве пробиотических бактерий, лактобацилл и бифидобактерий была обнаружена между группами вмешательства и плацебо / A non-significant difference in the total counts of probiotic bacteria, lactobacilli and bifidobacteria was found between the intervention and placebo groups
Chen et al., 2021 [86]	*Bifidobacterium longum CECT7894* + *Pediococcus pentosaceus CECT8330*	Значительное сокращение времени плача в группе вмешательства и улучшение консистенции стула / Significant reduction in crying time in the intervention group and improvement in stool consistency
Astó E. et al., 2022 [91]	*B. longum KABP042* + *P. pentosaceus KABP041*	Уменьшение тяжести симптомов у младенцев, страдающих коликами и/или запором на грудном и искусственном вскармливании / Reducing the severity of symptoms in breastfed and formula-fed infants with colic and/or constipation
Novikova V. P. 2023 [37] / Новикова В.П., 2023 [37] /	*Lactobacillus casei PXN 37, Lactobacillus rhamnosus PXN 54, Streptococcus thermophilus PXN 66, Lactobacillus acidophilus PXN 35, Bifidobacterium breve PXN 25, Bifido bacterium infantis PXN 27, Bifidobacterium longum PXN 30*; и пребиотик: ФОС (фруктоолигосахариды)	Купирование колик к 6-му дню, что раньше, чем при использовании *L. reuteri DSM 17938* (10-й день) и симптоматической терапии (12-й день). Увеличение уровня фекального зонулина на 44%, что больше, чем при использовании *L. reuteri DSM 17938* (40%) и симптоматической терапии (10%). Увеличение количества таких доминирующих представителей микробиоты, как эубактерии и пропионобактерии / Relief of colic by day 6, which is earlier than when using *L. reuteri DSM 17938* (day 10) and symptomatic therapy (day 12). Increase in fecal zonulin levels by 44%, which is greater than with the use of *L. reuteri DSM 17938* (40%) and symptomatic therapy (10%). An increase in the number of such dominant representatives of the microbiota as eubacteria and propionobacteria

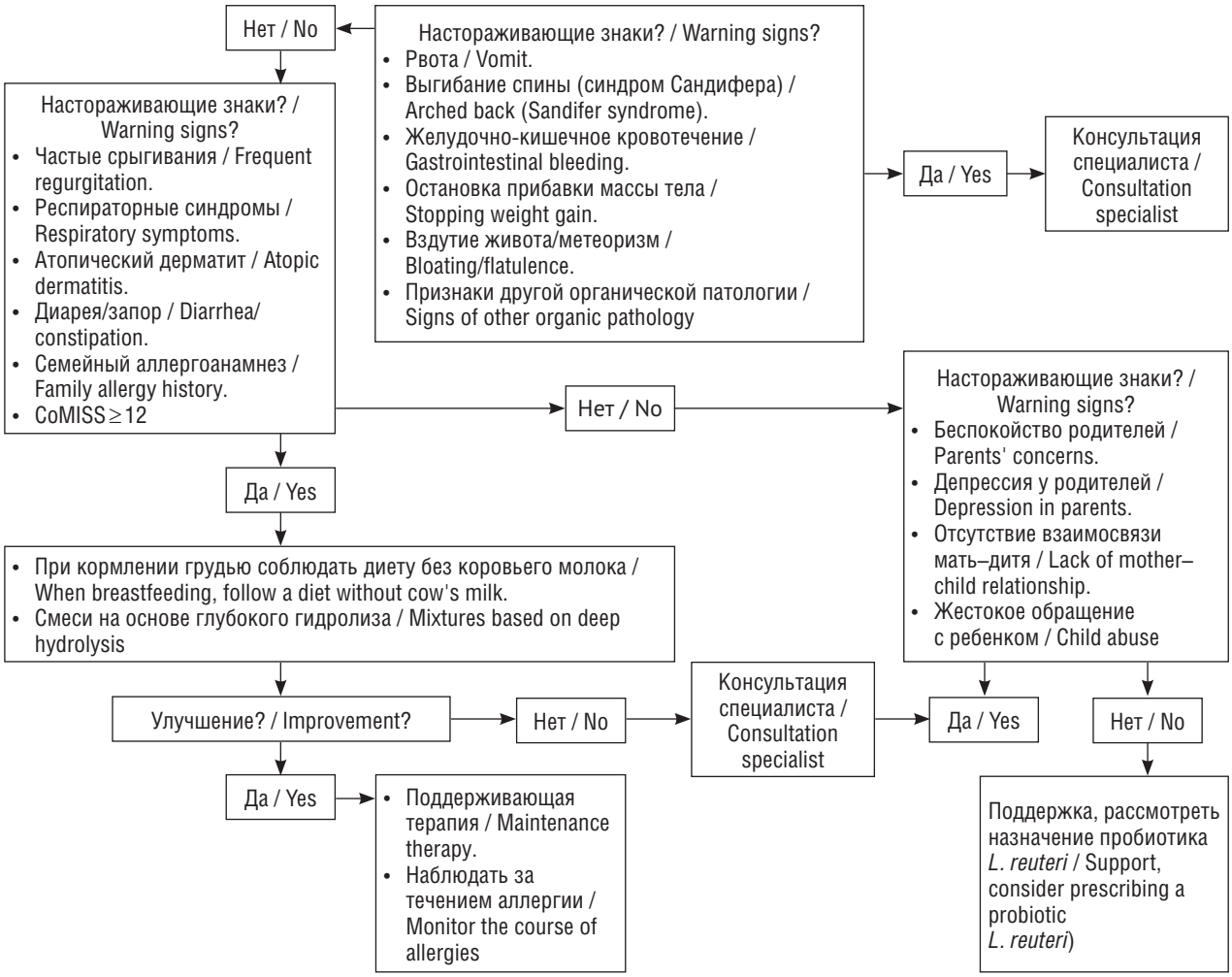

Fig. 1. Algorithm for diagnosing and treating colic (Vandenplas Y., 2016)
Рис. 1. Алгоритм диагностики и лечения колик (Vandenplas Y., 2016)

that the fetus hear in the womb hence it has a positive effect on the duration of crying and sleep in infants. However, there are limited studies that compare different treatments [37, 93].

Currently, the algorithm for diagnosis and treatment of colic proposed by ESPHAN (The European Society for Paediatric Gastroenterology Hepatology and Nutrition) experts in 2016 is generally accepted (Figure 1) [94].

Thus, infantile colic is a transient functional condition in children of the first 4–5 months of life that resolves on its own. However, it should always be remembered that serious pathologic conditions (gastrointestinal manifestations of food allergy, metabolic disorders, infectious processes, etc.) may hide under the mask of infantile colic, which requires differential diagnosis. Correction of IC symptoms is primarily based on psychological support of a family. With regard to breast-fed infants, breastfeeding support is mandatory, as well as the use of probiotics with proven anti-colic properties (Lactobacillus reuteri DSM 17938). Mothers are recommened to correct diet if food intolerance is suspected. In case an infant under 3 months old suffers from infantile colic, when breastfeeding is not feasible, it is preferable to use partially hydrolyzed whey formula with reduced lactose content and enriched with prebiotics. Additional, well-organized studies comparing different therapeutic strategies for colic are needed to develop optimal therapeutic approaches.

ADDITIONAL INFORMATION

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

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FEATURES OF THE COMPONENT COMPOSITION AND CALORIE CONTENT OF BREAST MILK IN OBESE MOTHERS

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Abstract. The article reviews the literature from 2013 to 2023, confirming changes in the composition of breast milk in obese women. It has been proven that in the breast milk of obese women, the content of lipids and the ratio of their fractions are changed, there are features in the composition of carbohydrate components (lactose and oligosaccharides of breast milk) in comparison with the breast milk of women with normal weight. There is also evidence of altered profiles of the hormones insulin, ghrelin, leptin and adiponectin, as well as microRNAs and immunological factors in the milk of obese mothers.

Key words: *breast milk; obesity; BMI; composition of breast milk; breastfeeding; epigenetics; calorie content of breast milk; overweight; components of breast milk.*

ОСОБЕННОСТИ КОМПОНЕНТНОГО СОСТАВА И КАЛОРИЙНОСТИ ГРУДНОГО МОЛОКА У МАТЕРЕЙ, СТРАДАЮЩИХ ОЖИРЕНИЕМ

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Резюме. В статье приведен обзор научных источников за период с 2013 по 2023 год, подтверждающий изменения состава грудного молока у женщин, страдающих ожирением. Доказано, что в грудном молоке женщин, страдающих ожирением, изменено содержание липидов и соотношение их фракций, имеются особенности состава углеводных компонентов (лактозы и олигосахаридов грудного молока) в сравнении с грудным молоком женщин, с нормальным весом. Имеются также данные об измененном профиле гормонов инсулина, грелина, лептина и адипонектина, а также микроРНК и иммунологических факторов в молоке матерей, страдающих ожирением.

Ключевые слова: *грудное молоко; ожирение; ИМТ; состав грудного молока; грудное вскармливание; эпигенетика; калорийность грудного молока; избыточный вес; компоненты грудного молока.*

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INTRODUCTION

Breast milk (BM) is a physiological source of nutrients for a child in the first year of life. The composition of the BM is unique and optimally adapted to meet almost all the needs of an actively growing organism up to 6 months. Breastfeeding (BF) is associated with lower mortality in infants than formula feeding. The UN and UNICEF argue that up to 10 million under-five deaths worldwide can be prevented every year by exclusive breastfeeding during the first six months of life [1]. The BM is a source of commencial bacteria that prevent the addition of pathogenic flora and contribute to the colonization of the intestine by useful microorganisms. The World Health Organization (WHO) recommends only BF for the first six months and as supplementary feeding until age 2.

The function of the BM is not limited to energy, and there is evidence of its immune, protective, epigenetic, and metabolic regulatory actions. The scientific evidence shows that the BM is an evolutionary factor for the optimal development of not only a healthy but also a sick child because the composition of the BM is capable of dynamic change, adapting to the needs of the child in a given situation.

The epigenetic effects of the BM are now highly relevant for study. It is becoming apparent that maternal nutrition and lifestyles can have a direct life-long impact on the child; it's called health programming. It is known that the BF is known to reduce the risk of many non-communicable pathologies, including obesity [2]. This is very important given the adverse epidemiological situation of the disease.

The global prevalence of obesity nearly tripled between 1975 and 2016. In 2014, the number of overweight and obese pregnant women was 38.9 million and 14.6 million, respectively, worldwide [3]. The prevalence of overweight and obesity among children and adolescents increased from 4% in 1975 to 18% in 2016 [4]. WHO estimates that more than 1.9 billion adults aged 18 years and over are overweight, of whom more than 650 million are obese. If current trends continue, the majority of the adult global population will be overweight or obese by 2030 [5]. It has been proven that BF prevents rapid weight gain in the neonatal period and reduces the propensity to develop obesity in adults, as opposed to formula feeding [6]. The usefulness of the BM may vary depending on its composition [7, 8]. The pathological conditions in the mother may influence the composition of the BM, but not much research has been published on this topic. There is proof that a mother's obesity prior to becoming pregnant increases the child's chance of obesity by three times [9]. Studies on animals have shown that ingesting a lot of fat during breastfeeding has an impact on the offspring's long-term obesity [10, 11]. An interesting question is the impact of maternal obesity on the calorie content and composition of the BM. The objective of this work is to review the current literature on the subject.

GENERAL INFORMATION ON THE COMPOSITION OF BREAST MILK

The human BM is a complex biological fluid containing a large number of components: macronutrients, hormones, biologically active molecules, stem cells, and microbial communities. Each of them is potentially responsible for a specific and synergistic impact on child health and the growth and development of organs and systems [12]. Lactose is the main carbohydrate in the human BM. Also, BM oligosaccharides (BMO) are important components of the BM. There are three main categories of BMOs: fucosilized neutral BMOs (35–50%), unfucosilized neutral BMOs (42–55%), and sialized acidic BMOs (12–14%). The primary source of energy is lipids, which are found in milk as an emulsion.

Triacylglycerides make up approximately 98% of the lipid fraction; 2% are phospholipids, monoacylglycerides, diacylglycerides, and free fatty acids. The human BM contains more than 400 different proteins, which can be divided into three main groups: casein, whey, and mucin proteins. The age of the child has a gradual effect on the protein ratio, which varies. Breast milk also contains non-protein nitrogen, which is up to 25% of the total nitrogen present in milk. In addition, the human BM contains the trace elements that the infant needs, except for vitamins K and D [13].

IMPACT OF MATHER'S OBESITY ON THE COMPONENTS OF MUTHER'S MILK

Summarizes the literature on the qualities of the component composition and calorie content of breast milk produced by obese moms in table 1.

Features of macronutrient content. The relationship between female obesity and changes in the composition and calorie content of the BM has been studied by many researchers. G.E. Leghi et al. did a large meta-analysis of the macronu-

trients found in the BM of normal-weight (NW) and overweight or obese women (OV/OW). They looked at colostrum, transitional milk, and mature milk. There was no difference in the concentration of fat in colostrum between OV/OW and NW. Also, in transient milk, the fat concentration was lower in OV/OW compared to NW. In mature milk, the fat concentration was higher in OV/OW than in NW. There was no discernible change in the protein concentration of the colostrum, transition, or mature BM between OV/OW and NW. The lactose concentration in colostrum was higher in OV/OW and NW. Nonetheless, there was no discernible variation in the lactose concentration between the transitional and mature BM samples [14]. The meta-analysis by A.I. Daniel et al. showed a positive relationship between the maternal body mass index (BMI) and the fat content of the BM. There is no discernible correlation between the mother's BMI and the amount of protein, lactose, or energy in milk [15]. Research findings about the lipid profile of the BM show that the milk of obese mothers has a higher ratio of ω-6 fatty acids (ω-6/ω-3 PUFA), a decrease in monounsaturated fatty acids (MUFA) and ω-3 in polyunsaturated fatty acids (PUFA), and an increase in saturated fatty acids (SFA) [16]. Based on a systematic review of most studies, it was found that moms who were overweight had higher levels of ω-6 PUFA and lower levels of ω-3 PUFA in their breast milk than eutrophic women [17, 18]. In the study by L. Ellsworth and others, there was no significant relationship between the ratio of ω-3 and ω-6 long-chain polyunsaturated fatty acids (LC-PUFA) in milk and the weight of the mother. But the content of palmitic, digomo-gamma-linolenic, and adrenal acids in milk was statistically significantly higher. The content of oleic and conjugated linoleic acids is lower in the OV/OW group. The same study did not reveal a significant difference in macronutrient content between groups of mothers [19]. PGE2 and LTE4 levels are not significantly different in groups NW and OV/OW [20]. Compared to women with NW, colostrum with OV/OW had higher levels of fat, glucose, and sIgA content, as well as more calories. There was no difference in the amounts of complement components C3 and C4, IgG, and IgM. [21]. The study by J.L. Saben et al. found that the BMI of nursing mothers was negatively correlated with the concentration of N-Neoserum radioactivity, disialyllacto-N-hexaose, fucosyllacto-N-hexaose, and total acid BMOs and positively correlated with the lacto-N-Neotetrazoma, 3-fucosylactose, 3-Sialillactose, and 6-Sialillactose concentrations [22].

Features of the content of biologically active compounds. Information on the hormone concentration in the body's BM, OV/OW, and NW varies. T.T. Guler and colleagues claim. In the BM group OV/OW, the grelin level before feeding was significantly higher than that of NW. In the BM group NW, after feeding, adiponectin levels were higher than those of OV/OW. There was no significant difference between the leptin and IGF-1 levels between the two groups [23].

In another study, the concentration of leptine in foremilk was correlated with the mother's BMI at 7 days and 3 months after delivery. Within three months of birth, there was a positive correlation between the mother's BMI and the BM's insulin. Grelin and BM resistine were not correlated with the mother's BMI [24]. According to the A. de Luca study, leptine content in OV/OW milk was higher than in NW milk, but macronutrient concentrations were the same [25]. There was no association found between BMI and adiponectin in the study by D. Chan et al., although there was a positive correlation between the mother's BMI and insulin and leptin [26]. Bioactive substances make up the BM, stem cells, and antibodies — particularly secretory immunoglobulins (sIgA and sIgG), including microRNAs — have drawn increasing attention in recent years. MicroRNA is a small, non-coding RNA molecule with a length of 18–25 nucleotides involved in transcription and posttranscriptional regulation of gene expression via RNA interference. The BM is one of the most miRNA-rich biological fluids, identifying about 1,400 species of miRNA. The study by K.B. Shah et al. found that the amount of miR-148a and miR-30b in the BM of women with OV/OW was 30% and 42% less than that of the NW group, respectively [27]. The following data on variations in leukocyte subsets in colostrum are intriguing for further research: In comparison to the control group, OV/OW has dramatically decreased the B-lymphocyte proportion in colostrum, and CD16 + blood monocytes have enhanced CD16 expression [28]. The concentration of lactoferrin in colostrum mothers with BMIs >30 kg/m^2 is noticeably higher than in mothers with normal BMIs [29]. There is proof that other non-specific protective variables have changed. It is known that a baby who is exclusively breastfed for the first year of their life may obtain up to 20% of the required daily allowance of vitamin D from the BM [30]. The way that the

Table 1. Features of the component composition and calorie content of breast milk in obese mothers (summary data)

Таблица 1. Особенности компонентного состава и калорийности грудного молока у матерей, страдающих ожирением (сводные данные)

Автор, год / Author, year	Тип исследования / Type of study	Популяция / Sample characteristic	Исследуемые показатели / Nutritional content analyzed	Результаты / Results
Mäkelä et al., 2013 [34]	Кросс-секционное / Cross-sectional	100 женщин, 49 НВ, 51 ОЖ / 100 women 49 NW, 51 OB	Уровень и состав жирных кислот / Fatty acid levels and composition	В молоке женщин с ИВ/ОЖ содержалось значительно больше НЖК и меньше ω-3 ПНЖК по сравнению с молоком женщин с нормальной массой тела. Соотношение ПНЖК и НЖК было ниже, а соотношение ω-6/ω-3 выше у ИВ/ОЖ / Overweight women had significantly more saturated fatty acids and lower omega 3 when compared to normal weight mothers. The proportion of unsaturated and saturated fatty acids was significantly lower, and the proportion of omega 6 to omega 3 was higher in overweight women
Fujimori et al., 2015 [21]	Когортное / A cohort study	68 женщин, 25 НВ, 24 ИВ, 19 ОЖ / 68 women 25 NW, 24 OW, 19 OB	Общий уровень липидов, глюкоза, белок / Total lipid levels, glucose levels, protein levels	В молозиве женщин с ИВ/ОЖ была повышена калорийность, содержание жиров и глюкозы. Содержание белков не отличалось / Calories, fat and glucose content were increased in the colostrum of overweight and obese women. Protein concentration was similar between groups
Daniel et al., 2021 [15]	Метаанализ / Meta-analysis	66 исследований, 4764 женщины / 66 studies 4764 women	Калорийность, содержание липидов, белков / Calories, lipid content, protein content	Имелась устойчивая положительная связь между ИМТ матери и содержанием жира в грудном молоке. Не было обнаружено ассоциаций между ИМТ матери и общим содержанием белка или энергии в грудном молоке / There was a consistent positive association between maternal BMI and breast milk fat content: No associations were found between maternal BMI and total protein or energy content of breast milk
Saben et al., 2020 [39]	Когортное / A cohort study	172 женщины / 172 women	Концентрация 115 известных и 240 ранее неизвестных метаболитов ГМ / Concentrations of 115 known and 240 previously unknown BM metabolites	Содержание 111 метаболитов было связано с ИМТ матери. Молоко матерей, страдающих ожирением, было обогащено моносахаридами и сахарными спиртами. Часть метаболитов, различающихся в зависимости от массы тела матери, были предикторами более высокой степени накопления жировой ткани у младенцев в течение первых шести месяцев жизни / The content of 111 metabolites was related to maternal BMI. The milk of obese mothers was enriched in monosaccharides and sugar alcohols. Some of the metabolites differing according to maternal weight were predictors of a higher degree of adipose tissue accumulation in infants during the first 6 months of life

Ending of the table 1 / Окончание табл. 1

Автор, год / Author, year	Тип исследования / Type of study	Популяция / Sample characteristic	Исследуемые показатели / Nutritional content analyzed	Результаты / Results
Leghi G. E. et al., 2020 [14]	Метаанализ / Meta-analysis	9 исследований, 872 женщины / 9 studies 872 women	Концентрация липидов, белков, лактозы в молозиве, переходном и зрелом ГМ / Concentration of lipids, proteins, and lactose in colostrum, transitional and mature BM	Не было выявлено различий в концентрации жиров в молозиве между ИВ/ОЖ и НВ. В переходном молоке концентрация жира была ниже у ИВ/ОЖ по сравнению с НВ. В зрелом молоке концентрация жира была выше у ИВ/ОЖ по сравнению с НВ. Различий в концентрации белка в ГМ между ИВ/ОЖ и НВ не было обнаружено в молозиве, переходном и зрелом ГМ. Концентрация лактозы в молозиве была выше у ИВ/ОЖ по сравнению с НВ. Не было обнаружено различий в концентрации лактозы в переходном и зрелом молоке / There were no differences in fat concentration in the colostrum between overweight/obese (OW/OB) and normal weight (NW) women. In transitional milk, fat concentration was lower in OW/OB compared to NW. In mature milk, the fat concentration was higher in OW/OB compared to NW. No differences in protein concentration in breast milk (BM) between OW/OB and NW were found in colostrum, transitional and mature BM. The concentration of lactose in the colostrum was higher in the OW/OB compared to the NW. No differences were found in lactose concentration in transitional and mature milk
Bardanzellu F. et al., 2021 [33]	Метаанализ / Meta-analysis	15 исследований / 15 studies	Производные нуклеотидов, 5-метилтиоаденозин, сахарные спирты, ацилкарнитин и аминокислоты, полиамины, моно- и олигосахариды, липиды / Nucleotide derivatives, 5- methylthioadenosine, sugar alcohols, acylcarnitine and amino acids, polyamines, mono- and oligosaccharides, lipids	В молоке матерей с ИВ/ОЖ по сравнению с молоком женщин с НВ уровень ПНЖК был значительно снижен, отмечено повышение уровня НЖК и/или снижение уровня МНЖК или изменение соотношения МНЖК/НЖК или ПНЖК/НЖК. Содержание метаболитов углеводного обмена было повышено по результатам большинства исследований. Обнаружено повышенное содержание шикимовой кислоты, лейцина, изолейцина, валина, глутамина, аспарагина, орнитина, тирозина, АМФ, аденина, мочевой кислоты, сахарных спиртов. Обнаружено снижение уровня кинуреновой кислоты, цАМФ, общего уровня полиаминов, спермидина, утресина / ω-3 PUFAs were significantly reduced in the milk of mothers with OW/OB compared to NW, there was an increase in SFAs and/or a decrease in MUFAs or a change in the ratio of MUFAs/SFAs or PUFAs/SFAs. The content of carbohydrate metabolites was elevated in most studies. Shikimic acid, leucine, isoleucine, valine, glutamine, asparagine, ornithine, tyrosine, AMP, adenine, uric acid, and sugar alcohols were elevated. A decrease in kynurenic acid, cAMP, total polyamines, spermidine, putrescine was found

vitamin D concentration of women with BM obesity varies is not well studied. However, research indicates that mothers with NW had higher serum concentrations of 25(OH)D than obese women do. In babies born to mothers with OV/OW, the serum concentration of 25(OH)D was reliably lower than in infants with NW [31].

Metaboloma Features. Metabolomics is regarded by many as the most promising technique for examining variations in the composition of BM in women with different diseases, including obesity. There are several expert groups working on this right now. Metabolom is a complete set of low molecular metabolites — metabolites, hormones, and other signaling molecules — and secondary metabolites. As per the research conducted by E. Isganaitis and colleagues, The breast milk of the OV/OW and NW groups differed in terms of metabolite content one month after delivery; 3 out of 10 metabolites were human milk oligosaccharides and 4 out of 10 were nucleotide derivatives. There was a positive correlation found between the BMI of the mother and the accumulation of fat in the infants. A composition study of 20 milk metabolites had different contents six months after delivery. At 1 and 6 months, the mother's BMI was favorably correlated with the 1.5-anhydrocytol content of human milk, which had not before been reported in milk [32].

F. Bardanzellu and co-author conducted one of the largest studies on the metabolomics of BM [33] by conducting a meta-analysis of numerous publications and considering the characteristics of the composition of BM in overweight or obese women. In general, a significant increase in the ratio of ω-6/ω-3 was observed in the colostrum, transition, and mature milk of mothers with OV/OW. In all but one of the studies included in the analysis, the level of ω-3 PUFA was significantly reduced in the group of mothers with OV/OW. A few studies [34–37] also reported changes in the ratios of MUFA/SFA or PUFA/SFA, as well as a rise or decrease in the level of SFA. In most studies, women with OV/OW have been promoted based on the content of carbohydrate metabolites such as mannose, d-xylose (in the form of its main derivative, xyloloctone), ribose (the essential component of DNA, RNA, acetyl coenzyme A, and ATP), lycose, glucose-6-phosphate, and 1,5-angydrucitol (1,5-AGH) in the BM.

It is also intriguing that the BM women with OV/OW had elevated shikimic acid. In a study in vitro [38], shikimic acid was discovered to diminish lipid buildup in hepatocellular carcinoma cells and adipocytes. This metabolite displayed anti-inflammatory and antioxidant characteristics in animal models. In the examination of amino acid composition in the BM, numerous amino acids (leucine, isoleucine, valine, glutamine, asparagine, ornithine, and tyrosine) were shown to be different in the NW and OV/OW groups [32, 39]. In the study by A. de Luca et al., there is evidence that the mature milk of obese women includes 20% more branched-chain amino acids and 30% more tyrosine than that of eutrophic women [40]. Notably, increasing branched-chain amino acids can change insulin production and insulin sensitivity, which can lead to obesity in children and adolescents [41]. 6 months after delivery, the amount of kynurenic acid is lowered by around 30% in the group of mothers with OV/OW [32]. This acid is generated as a result of tryptophan catabolism, and tryptophan-kynurenine metabolic pathway disruption is considered to promote obesity [42]. Among the purine derivatives in the BM of women with OV/OW at the 1st month of breastfeeding, a rise in adenosine monophosphate and its catabolite adenine and a decrease in cyclic adenosine monophosphate [32] were found. Saben et al. identified an increase in uric acid in breast-milk women with obesity at 6 months of breastfeeding [39]. Increased purine exchange can promote weight gain long after birth. At the same time, it enhances glucose tolerance and insulin sensitivity during obesity, as well as lowers cardiovascular risk [33]. Polyamines of putressin and spermidine (and total polyamine levels) have been reduced in the BM of women with OV/OW, according to the study by Ali et al. [43]. Some research on mouse obesity models [44, 45] demonstrates that higher levels of polyamines in white adipose tissue, liver, and skeletal muscles boost energy consumption, resisting obesity. They are essential in the early stages of adipocyte differentiation in adipocyte tissue because they alter the expression levels of transcription factors involved in the regulation of adipogenesis at the preadipocyte level [46]. These findings suggest that the long-term effects of the BM's decreased polyamine levels may include adverse effects on body weight gain. The amount of erythrol, arabitol, rabitol, and glycerine sugar alcohols in the BM of moms with OV/OW has increased. Hootman et al. [47] consider erythrol to be one of the possible indicators of obesity. There is one case-control study

that demonstrates a connection between maternal obesity and elevated arabitol in infants [48].

CONCLUSION

The changed composition of the BM may be a factor potentially affecting a child born to a mother with obesity. 48 research that assessed the distinctions in breast milk between women who are overweight or obese and those who are of normal weight, either directly or indirectly, were analyzed. There are differences in the macronutrient content, micronutrients, metabolites, and biologically active substances in the breast milk of obese women. These data serve as the foundation for further thorough research because single experimental investigations have not yet provided a good understanding of the mechanisms behind the consequences of these alterations on children's health. A thorough examination of the metabolic traits of children born to obese mothers is necessary to determine the causal linkages between alterations in the composition of breast milk and the corresponding advantages or risks. Investigating how obese moms' diets and lifestyle changes affect the makeup of their breast milk could be one pathway for future research.

ADDITIONAL INFORMATION

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

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MODERN CONCEPTS ON THE BIOLOGICAL ROLE AND CLINICAL SIGNIFICANCE OF CLAUDINS

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Abstract. At present, sufficient data and information have been accumulated on changes in claudins levels in various gastroenterological diseases. However, the issue of claudins content in intestinal pathologies remains poorly studied. Currently, post-giardiasis inflammatory bowel disease (IBS) is being actively studied. According to Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) in the Russian Federation, giardiasis ranks second after enterobiosis. Every year, up to 70–75% of children under the age of 17 fall ill with it. In addition, there is evidence that 5 to 10% of children diagnosed with IBS were previously infected *Lamblia intestinalis*. Giardiasis attacks the intestinal barrier and promotes the degradation of tight junction proteins such as Zo-1, claudin-1 and claudin-4. Claudins levels were decreased due to damage to the intestinal barrier. The role of excess claudins in IBD remains controversial. The studies examine the positive and negative effects of claudine-isoform levels on the human body depending on conditions. In addition to diseases, the level of claudins also depends on the content of cytokines.

Key words: *claudin; giardiasis; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD); intestinal barrier.*

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О БИОЛОГИЧЕСКОЙ РОЛИ И КЛИНИЧЕСКОМ ЗНАЧЕНИИ КЛАУДИНОВ

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Резюме. На сегодняшний день накоплено достаточно сведений и информации об изменениях уровня клаудинов при различных гастроэнтерологических заболеваниях. Однако до сих пор остается малоизученным вопрос содержания клаудинов при кишечных патологиях. В настоящее время ведется активное изучение постлямблиозного синдрома раздраженного кишечника (СРК). По данным Роспотребнадзора, в Российской Федерации лямблиоз занимает второе место после энтеробиоза. Ежегодно им заболевают до 70–75% детей в возрасте до 17 лет. Кроме того, имеются данные, что от 5 до 10% детей с выявленным СРК были ранее инфицированы *Lamblia intestinalis*. Лямблиоз поражает кишечный барьер и способствует деградации белков плотных контактов, таких как Zo-1, клаудин-1 и клаудин-4. Уровень клаудинов был понижен в связи с поражением кишечного барьера. Вопрос о роли избыточного содержания клаудинов при ВЗК остается спорным. В исследованиях рассматриваются положительные и негативные влияния уровня изоформы клаудина на организм человека в зависимости от условий. Помимо заболеваний, уровень клаудинов зависит также от содержания цитокинов.

Ключевые слова*: клаудин; лямблиоз; синдром раздраженного кишечника (СРК); воспалительные заболевания кишечника (ВЗК); кишечный барьер.*

INTRODUCTION

The primary constituents of the dense compounds found in the epithelial cells of vertebrates are several integral membrane proteins belonging to the claudine family [1]. Dense compounds, also known as contacts, are complex structures that operate as a paracellular barrier between the apical and basolateral regions of the plasma membrane, regulating specific permeability and preserving cellular polarity.

Claudines consist of four transmembrane α-helices, two extracellular loops with variable amino acid sequences, and short cytoplasmic N- and C-ends. Extracellular loops, notably the first, participate in the creation of ionoselectic channels due to homophilic and heterophilic contacts between claudines on adjacent cell membranes [2]. There are now 27 known kinds of claudines. The full range of functions of these proteins is unknown and continues to be studied. Lal-Nag and M. Morin demonstrated that transdermal water loss caused dehydration in mice harboring Claudin-1. [3, 4]. In mice lacking claudine 11 and 14, the loss of dense connections from the basal cells of the vascular strip resulted in the development of deafness. Due to the loss of nerve conductivity along peripheral myelinated fibers and Schwann cell densities, claudine-19 deficiency resulted in behavioral abnormalities. According to other research, individuals with inflammatory bowel disease (IBS) have lower levels of claudine-1 protein expression, which is correlated with the illness's protracted course [5, 6]. The diversity of claudines thus points to a critical role for them in the control of paracellular transport and the operation of dense connections. The link between claudine structure and function, expression regulation mechanisms, and the pathological consequences of dysregulation of these dense contact proteins (DCP) are the subjects of an increasing amount of research. Determining the DCP level for different diseases is of some importance.

INFLAMMATORY BOWEL DISEASE

One of the most frequent bowel pathologies are inflammatory bowel disease (IBD) — Crohn's disease (CD) and ulcerative colitis (UC). It has been suggested that a change in the level of Claudine plays a role in the pathogenesis of IBD [7]. Indeed, the anomalies of most of the claudin isoforms lead to impaired intestinal barrier functions [8]. A number of studies have been conducted on patients with UC and CD [9]. Changes in the level of claudine under the IBD were detected based on a study of the intestinal epithelium biopsy material. Ulcerative colitis increased the expression of claudine-1, -2 and -18 and lowered the regulation of claudine-3, -4 and -7. CD also showed elevated levels of claudine-1 and claudine-2 and decreased expression of claudine-3 in the intestine epithelium [10].

In their study, Preeti Raju and Nitesh Shashikanth conclude on the pathogenic role of elevated level of claudine-2 in the development of colitis and try to solve this problem by exposure to casein kinase-2 [11]. The authors argue that such a solution requires further research and could be used as a CMV therapy. However, there is a contrary view. C.T. Capaldo and Claudin Barriers have shown resistance to colitis at high levels of claudin [12]. This hypothesis was demonstrated in an experiment with mice that were transgenically modified for increased production of claudine-2. Claudine-2 was later shown to be protective of chemically induced and pathogen-induced colitis. In places with pathologies such as immuno-mediated colitis, high levels of claudine-2 exacerbate the disease, and the removal of this isoform of claudine is beneficial.

Other isoform studies suggest the important role of Claudines in the IBD — participation in cell proliferation and migration at the cellular level. However, claudine-2 increases the flow of antigens to different tissues. This may be due to the effect of claudine-2 expression on cell division. If the damage is due to a pathogen, high levels of claudine-2 can have a positive effect by accelerating regeneration processes. However, in case of chronic damage, the increased isoform content is destructive due to the enhanced action of antigens. Thus, the elevated content of claudine may in different cases indicate beneficial and pathogenic changes [13].

To diagnose inflammatory bowel disease, it is essential to determine the level of claudine. Some studies show a relationship between dense contact lesions and the level of claudine-3 in urine in patients with IBD. In this pathology, the level of claudins in urine is increased dramatically [14, 15].

In addition to inflammatory bowel diseases, the content of claudine also varies with irritable bowel syndrome. According to some reports, the expression of claudine-1 decreases in patients with IBS [16].

IRRITABLE BOWEL SYNDROME

The IBS is a set of functional impairments that include abdominal pain, lessening after the act of defecation, occurring at least three days per

month during the last three months, with a total duration of at least 6 months [17]. It has been proven that the level of claudine-1 in patients with IBS with diarrhea is lowered [18, 19].

Some cytokines play an important role in changes in the level of claudine under the IBS. Tumor necrosis factor alpha (TNFα) and interferon-gamma contribute to the degradation of dense contacts by affecting the claudins. These cytokines are often found in tests of patients with IBS. Thus, cytokines are involved in altering the epithelial barrier by affecting claudine [20, 21]. A study by V. Ivashkin and Y. Poluektov demonstrates changes in cytokines and claudins at IBS [22].

A number of conclusions were drawn from the data. In IBS, a statistically significant increase in the expression of flammable cytokine TNFα and cytokine IL-2 is detected. The anti-inflammatory cytokine IL-10 content in the bioptat was significantly reduced, as was the content of claudine-3, -5 [23, 24]. The authors suggest that the level of claudine is reduced by the degranulation of mast cells due to the release of tryptase. In addition, degranulation causes the release of inflammation mediators and activates lymphocytes, resulting in cytokine imbalance [25].

AFTER GIARDIASIS IRRITABLE BOWEL SYNDROME

Giardiasis is one of the most common diseases in the world. The causative agent is Giardia lamblia, transmitted by fecal-oral via direct or indirect contact of the parasite cysts with water and food [26, 27]. Symptoms of giardiasis may be absent or exhibit acute watery diarrhea, nausea, epigastric pain [28–30].

Infection of Lamblia intestinalis can provoke the development of post-exposure IBS, contributing to the destruction of the intestinal barrier. A number of studies have been carried out on newborn mice with exogenous infection. Hypersensitivity syndrome was found in mice 50 days after infection, due to nausea, crypt hyperplasia and increased immune cell count. The work also found an intercellular bacterial translocation through the epithelial barrier, which can be observed with giardiasis [31]. In addition, the authors concluded that giardiasis causes persistent damage to dense contacts, especially claudin. Bacterial translocation was associated with increased neutrophilic infiltration. Proinflammatory cytokines also played a key role in the process, with an increased number of them. For example, mice showed elevated levels of interferon-α and interferon-γ, TNF, and IL-1 [32]. Thus, bacterial inflammation may persist after the removal of giardia for a long time, which may contribute to the development of post-infectious intestinal disorders [33].

Other studies found a high prevalence of giardiasis infection in patients with IBS in duodenal biopsy and stool research. The authors conclude that infection of Lamblia intestinalis may be one of the possible causes of symptoms in patients with IBS [34, 35]. There are also studies showing inverse relationships. Many patients diagnosed with IBS are susceptible to infection with Lamblia intestinalis [36]. At the same time, the change in the level of clausines in the case of a post giardiasis IBS remains an issue of discussion.

CONCLUSION

Thus, varied claudine contents are shown by these illnesses; yet, claudine can still be harmful and speed up the progression of sickness. The problem was not thoroughly investigated and needed to be given more careful thought. Nonetheless, claudins play a significant diagnostic function in gastrointestinal diseases, and physicians should modify the course of treatment for patients with IBD and IBS based on their claudine levels.

ADDITIONAL INFORMATION

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

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

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

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

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

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ESOPHAGEAL DYSPHAGIA: CLINICAL PICTURE, DIAGNOSIS, TREATMENT. LITERATURE REVIEW

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Abstract. Dysphagia (difficulty swallowing) is a violation of the normal passage of swallowed food at the beginning of swallowing or when passing through the esophagus. There are oropharyngeal and esophageal types of dysphagia. Dysphagia or malnutrition is always associated with a high risk of medical complications, being a predictor of poor functional recovery and increasing the risk of sudden death. Esophageal dysphagia can be caused by various diseases, anatomical abnormalities of the digestive tract, and neuromuscular disorders. The review presents the clinical manifestations, diagnosis and treatment of esophageal dysphagia.

Key words*: esophageal dysphagia; diagnosis of dysphagia; treatment of dysphagia.*

ПИЩЕВОДНАЯ ДИСФАГИЯ: КЛИНИКА, ДИАГНОСТИКА, ЛЕЧЕНИЕ. ОБЗОР ЛИТЕРАТУРЫ

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Резюме. Дисфагия (затруднение глотания) — это нарушение нормального прохождения проглатываемой пищи в начале глотания или при прохождении по пищеводу. Выделяют орофарингеальную и пищеводную виды дисфагий. Дисфагия или недостаточность питания всегда ассоциируются с высоким риском медицинских осложнений, являясь предиктором плохого функционального восстановления и увеличивая риск внезапной смерти. Пищеводная дисфагия может быть вызвана различными заболеваниями, анатомическими аномалиями отделов пищеварительного тракта, нервно-мышечными расстройствами. В обзоре представлены клинические проявления, диагностика и лечение пищеводной дисфагии.

Ключевые слова: *пищеводная дисфагия; диагностика дисфагии; лечение дисфагии.*

INTRODUCTION

Dysphagia (difficult swallowing) is a disturbance of the normal flow of food at the beginning of swallowing or when passing through the esophagus. Dysphagia is a common complaint, the frequency of which varies between adults and children, as they have a different disease spectrum. According to some data, the incidence of dysphagia in case of emergency may reach more than 30% of cases [1].

Dysphagia is a life-threatening disorder, as patients with dysphagia are at increased risk of

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malnutrition and withdrawal, cachexia, aspiration pneumonia, and obstruction of the respiratory tract [2–5]. Dysphagia is also associated with increased risk of death, poor quality of life, increased disability and longer hospital stays [3, 6, 7]. Dysphagia of any degree affects the nutritional status of the patient and is the most important cause of progression of protein-energy deficiency (PED) in children with infantile cerebral palsy (ICP) [4, 8, 9]. Dysphagia also significantly worsens the prognosis and complicates the rehabilitation of the patient [3].

Dysphagia is increasingly found in paediatric practices, especially as advances in health improve the survival of extremely premature children and children with complex congenital abnormalities [10]. Infancy and childhood are times of physical growth and cognitive development. In order for children to develop fully, they must be able to consume sufficient energy and nutrients safely and securely. Difficulty swallowing (dysphagia) in children can have a detrimental effect on food consumption and thus on growth and development [11]. Infants and children with nutritional difficulties are at high risk of aspiration, which can lead to recurrent aspiration pneumonia and chronic respiratory diseases [12]. As a result, it is essential to accurately identify and properly treat dysphagia in the paediatric population [11].

Prevailing global trends in the study of dysphagia and growing public awareness of the quality of life and its far-reaching implications for health suggest that research on dysphagia will gain further popularity [13]. Registers of patients suffering from dysphagia as well as gastronomic children with possible causes of gastrostomy are being established [14, 15].

MATERIALS AND METHODS

Using PubMed and elibrary bases using the keywords "esophageal, dysphagia, esophageal, dysphagia" found 2196 sources. The analysis selected 53 sources for review.

DEFINITION

The term "dysphagia" is commonly used to describe the subjective sensation of having difficulty swallowing during a bolus going from the mouth to the stomach or feeling obstruction when swallowing [16]. In clinical practice, it is more accurately described as the feeling of food or fluid stuck in the esophagus or thorax [17]. Dysphagia is seen as an obstruction in a person's initial swallowing (usually defined as rotoglobulic dysphagia) or a sense of an obstruction of food or fluid from the oral cavity to the stomach (usually defined as esophageal dysphagia) [18]. Esophageal dysphagia is called the lower, because the unpleasant sensations and their causes are related mainly to the lower part of the esophagus [1].

AETIOLOGY

Dysphagia (abnormal swallowing) can be the result of a wide range of diseases and disorders [2, 5]. Dysphagia is the most characteristic symptom lesion of esophageal [23].

There are several major states that are most common to esophageal dysphagia [1]: obturation of the esophagus lumen by the foreign body (often causes acute dysphagia) [24, 25]; lesion of the mucosa, which leads to narrowing of the lumen due to inflammation, fibrosis or neoplasia [26]:

- gastroesophageal reflux disease (esophageal peptic stricture) [1, 18, 24, 25];
- sidereal dysphagia or Plummer-Vinson syndrome (esophageal rings and connecting membranes) [22];
  - esophageal tumors, chemical lesions (ingestion of caustic fluids, medicinal esophagitis, sclerotherapy of esophageal varicose veins) [1, 2, 18];
  - radiation injuries, infectious esophagitis;
- mediastinum diseases that cause esophageal obstruction by direct invasion or by increasing lymph nodes [22]:
  - tumors (including lung cancer, lymphoma) [26];
  - infections (including tuberculosis, histoplasmosis);
  - cardiovascular diseases (atrial dilation, aortic aneurysm) [22];
- neuromuscular diseases affecting the smooth muscles of the esophagus and the submucosal nervous plexus disrupting the peristaltic thoracic region of the esophagus or lower esophageal sphincter (LES) or both [1, 27, 28]:
  - cardia achalasia [1, 29];
  - scleroderma [22];
  - other motor disorders (esophagospasm, cardiospasm);
  - esophageal diverticular [22];
  - post-surgical condition (fundoplication and other anti-defects) [1].

Problems with salivation, swallowing and feeding are observed in premature children, children with perinatal brain damage, after ischemic stroke and intraventricular bleeding [6, 30], patients with

cerebral palsy, in children with soft and hard palate crevices, laryngomalacia, patient with tracheostomy cannula, after prolonged intubation. Dysphagia in children is more common among patients with cerebral palsy [4, 14]. According to some authors, up to 46% of cases of dysphagia in children are patients with cerebral palsy [14, 22]. Difficulties in eating and drinking are also recognized sources of ill health in people with dementia [7].

Pronounced symptoms of dysphagia are characteristic of patients with eosinophilic esophagitis, which is becoming increasingly common [22, 27, 29, 31]. The incidence of dysphagia when eating solid consistency in such patients is 29–100% [32].

Esophageal dysfunction caused by opioids is becoming increasingly common [27].

Functional dysphagia (FD) is the most rare disorder (less than 1%) [18].

Refractory psychogenic dysphagia as functional laryngeal-pharyngeal disorder [33] has been increasing over the past few years.

Dysphagia should not be confused with the feeling of a "lump in the throat", which is not related to the act of swallowing and food flow disturbance [34, 35].

EPIDEMIOLOGY

Based on limited data, the prevalence of dysphagia in the general population is estimated at around 20 per cent and is estimated to be 50 to 66 per cent of people over 60 years of age. Dysphagia is more common in women than in men in all age groups. Elderly, stroke patients with a history, Alzheimer's disease or lateral amyotrophic sclerosis are more likely to complain about dysphagia. In younger people, dysphagia is often associated with a major systemic disease such as autoimmune diseases, gastroesophageal reflux disease (GERD) or eosinophilic esophagitis [36].

The incidence of dysphagia in the provision of emergency medical care reaches 33%, and the analysis of data on home care shows that 30-40% of patients have abnormalities of swallowing, which lead to a large number of aspiration complications [18].

Esophageal dysphagia is less common, 15–20% of cases [37].

CLINICAL PICTURE

Clinical signs of abnormality in the esophageal phase of swallowing: the sensation of "sticking" food behind the breasts, regurgitation [38].

Esophageal dysphagia may be accompanied by salivation, but not as pronounced as in oropharyngeal dysphagia. It is typical of hoarse-elk and voice-age, especially after sleep. Patients may complain about the sensation of a "lump in the throat", the feeling of a lump of food in the throat or esophagus, heartburn and burping, pain in the upper abdomen and behind the sternum. The chest pains may be quite severe and tend to increase. The appearance of a severe reflex cough is a consequence of the throwing of food masses into the larynx and trachea. As a rule, patients are forced to drink any food [37]. Some esophageal dysphagia patients, caused by cardia achalasia, may complain of difficulty swallowing in the cervical portion of the esophagus, which mimics oropharyngeal dysphagia. Esophageal dysphagia occurs equally after ingestion of both solid and liquid foods, often leading to suspicions of motor esophageal disorders. This suspicion is heightened when intermittent dysphagia is accompanied by chest pains in both solid and liquid foods [22].

Patients also suffer loss of body weight, nutritional status change [3, 9].

In children with gastroesophageal reflux disease, dysphagia is more common intermittently and occurs in the early stages of the disease, usually due to hypermotor esophageal dyskinesia [2].

Appearance of persistent dysphagia with simultaneous reduction of heartburn may indicate formation of esophageal stricture [39].

DIAGNOSIS

Diagnosis of dysphagia — multi-stage process [40]. Examination of a patient with dysphagia requires structured assessment to identify functional, neurological, inflammatory and malignant causes [36, 41].

Diagnosis of swallowing disorders is multifaceted and includes anamnestic method, methods of clinical examination (neurological examination of soft palate in rest and background, determination of palate or throat reflexes, swallowing test) as well as tools [20, 41].

Collecting a clinical history helps determine the type of dysphagia and can guide diagnostic testing. Important questions to ask patients with a disorder include specific features of dysphagia, its onset and progression, associated problems and eating habits taken to alleviate symptoms [28].

It is advisable to test the ingestion act and the off-road consistency of various foods together with a swallowing specialist or clinical speech therapist. It is necessary to pay attention to the fear of a sip in the patient, the leak of food, liquids and

saliva, unusual position when swallowing. If there is productive contact with the patient it is possible to identify complaints of pain when swallowing and refusal of certain dishes and drinks [22].

Assessment of the patient's ability to swallow is necessary at any stage of the patient's follow-up, especially for those showing signs of dysphagia, in order to prevent more serious complications such as aspiration and the risk of death [42].

Patients with esophageal dysphagia should be referred to upper esophageal endoscopy, as this test will help eliminate mechanical obstruction or inflammation, or provide evidence that it may be esophageal dysfunction. In fact, almost every algorithm aimed at treating esophageal symptoms begins with an endoscopy of the upper esophagus, as this will determine the curable etiology and eliminate malignant neoplasm [10, 17, 27, 29, 43].

Endoscopic examination allows detailed examination of mucous membrane condition, esophageal permeability, the presence of fistula, diverticulum, etc. The undeniable advantage of endoscopic examination is its functionalities to simultaneously use additional diagnostic and therapeutic capabilities [40, 44]. Endoscopy serves as a test of choice in case of suspicion of obstruction or gastroesophageal reflux disease, since biopsy can confirm the presence of esophagitis and provide specific pathological identification of obstructive lesion [28].

Contrast X-ray examination of the esophagus with barium [17, 20, 22, 27] may also be required for differential diagnosis. X-ray examination with contrast is available, safe and informative enough, and the combination of fluoroscopy and roentgenography reveals not only morphological but also functional changes [40]. X-ray examination of esophagus is additionally carried out for differential diagnosis of GERD with other organic lesions of esophagus, for diagnosis of complications of GERD, such as esophageal stricture and esophageal tumor, for detection of secondary disorders of esophageal motor function [18]. X-rays examinations can be used to assess esophagus for structural abnormalities (e.g., membranes, diverticula, strictures, neoplasms) and to assess function (e.g., swallowing mechanism and esophageal motor). A thorough X-ray assessment with an individual approach can help to avoid misdiagnosis [16, 43].

If, after an X-ray and endoscopic examination, an obvious source of dysphagia is not identified, the possibility of manometry to detect possible motor dysfunction should be considered [22, 28, 43, 45]. Highresolution manometry (highresolution manometry — HRM) is a state-of-the-art high-tech esophageal motor function research method. HRM is used to diagnose most esophageal diseases in which there are functional motor disorders. The examination is mandatory for patients who complain about dysphagia, in order to identify motor impairments of the LES and throat [17, 46]. When carrying out esophageal manometry in patients with dysphagia, chest pain may detect other (except achalasia) disorders of the esophagus peristaltic, accompanied by premature contractions or hypercontraction's, such as hypercontractile esophagus and distal esophagospasm [47]. It is also possible to define fragmented, ineffective peristalsis or its absence as possible causes of dysphagia symptom formation [48].

To exclude eosinophilic esophagitis, the esophageal mucosal bioptat is studied [49]. A daily pH-metre of the esophagus is performed if the patient complains of heartburn and the GERD [18] must be deleted.

TREATMENT

Proper treatment depends on the cause of dysphagia [10].

In older children with classic GERD symptoms, an empirical prescription of proton pump inhibitors (PPI) within 4-8 weeks is warranted. PPI play a key role in the treatment of GERD, but have not been found useful in infants with GER [50].

Patients with eosinophilic esophagitis are shown local steroid therapy [17].

Endoscopic methods of esophageal and esophageal anastomosis recovery are effective and safe and have a low frequency of complications [51].

The main trend today is the use of minimally invasive endoscopic methods. Thus, in the presence of esophageal strictures and anastomoses, various types of explosions, balloon dilation, electric dissection, stenting and operative treatment are used [40].

Esophageal endoprosthesis in case of stenosis or compression from outside is a low-traumatic, safe and effective intervention. Endoprosthesis by self-healing stents ensures a sufficiently wide clearance of the digestive tube, nutritional nutrition, as a rule, does not require repeated therapeutic interventions, thus improving the quality of life of this category of patients [52].

Rehabilitation is shown for all patients with dysphagia in CNS diseases. Patients require supervision and multidisciplinary team treatment and rehabilitation, including nutritional support, physical training and physiotherapy, speech therapy, pain therapy, psychological correction [53].

The treatment of functional dysphagia includes an explanation of the disease, its transient nature and favorable prognosis, as well as the following recommendations: avoid provoking factors, eat upright, thoroughly chew food and drink it. Sometimes IPP, antidepressants [1] can be effective.

CONCLUSION

Esophageal dysphagia is a common pathology in the practice of doctors of various specialties. Dysphagia has an extremely negative impact on the quality of life, leads to severe complications of the respiratory system, causes dehydration, energy metabolism disorders, cachexia and aggravation of disability. It significantly worsens the prognosis and complicates the rehabilitation of the patient. It should be borne in mind that dysphagia or malnutrition are always associated with a high risk of medical complications, being a predictor of poor functional recovery and increasing the risk of sudden death. Dysphagia can be caused by many diseases, anatomical abnormalities in the digestive tract, and neuromuscular disorders. In diagnosis, the most common methods, in addition to the interpretation of symptoms, medical history and physical assessment, are endoscopy, barium X-ray and esophageal manometry. Treatment approaches depend on the etiological cause of esophageal dysphagia and include both conservative and operative methods.

ADDITIONAL INFORMATION

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

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COLLAGENS IN THE GASTROINTESTINAL MUCOSA: PEDIATRIC ASPECTS

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Abstract. The spectrum of collagen diseases of the digestive tract is diverse and is divided into three categories: collagenous gastritis, collagenous sprue (collagen enteritis) and collagenous colitis. According to N. Nyhlin et al. (2006), the total annual incidence of CC in the adult section is 4–6 cases per 100,000 people, being one of the causes of chronic diarrhea in elderly patients. It is known that in pediatric practice, the most common form is collagenous gastroenteritis, which is often the cause of severe iron deficiency anemia, which reacts to oral iron supplements, but may recur after drug withdrawal. The disease can be considered as a new possible cause of severe iron deficiency anemia and abdominal pain in children, therefore it is an urgent topic for randomized trials today. The literature review presents data from the analysis of scientific publications of compatriots and foreign colleagues related to collagen diseases in children, in order to increase awareness and alertness about the pathology.

Key words: *collagenous gastritis in children; chronic gastritis; collagenous colitis; microscopic colitis; collagenous sprue; severe iron deficiency anemia in children.*

КОЛЛАГЕНЫ В СЛИЗИСТОЙ ОБОЛОЧКЕ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА: ПЕДИАТРИЧЕСКИЕ АСПЕКТЫ

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Резюме. Спектр коллагеновых заболеваний пищеварительного тракта разнообразен и делится на три категории: коллагеновый гастрит, коллагеновая спру (коллагеновый энтерит) и коллагеновый колит. По данным N. Nyhlin и соавт. (2006), общая годовая заболеваемость коллагеновый колитом во взрослой популяции составляет 4-6 случаев на 100 000 человек, являясь одной из причин хронической диареи у пожилых пациентов. Известно, что в педиатрической практике наиболее встречающейся формой является коллагеновый гастроэнтерит, нередко являющийся причиной тяжелой железодефицитной анемии, которая реагирует на пероральные добавки железа, однако может рецидивировать после отмены препаратов. Заболевание может рассматриваться в качестве новой возможной причины тяжелой железодефицитной анемии и болей в животе у детей, потому является актуальной в настоящее время темой для проведения рандомизированных исследований. В литературном обзоре представлены данные анализа научных публикаций

соотечественников и зарубежных коллег, связанных с коллагеновыми заболеваниями у детей, с целью большей осведомленности и настороженности по поводу данной патологии.

Ключевые слова: *коллагеновый гастрит у детей; хронический гастрит; коллагеновый колит; микроскопический колит; коллагеновая спру; тяжелая железодефицитная анемия у детей.*

The spectrum of collagen diseases of the digestive tract is diverse and is divided into three categories: collagen gastritis (CG), collagenous sprue (collagen enteritis — CE) and collagen colitis (CC) [1]. N. Nyhlin et al. (2006) report that the adult population's overall yearly incidence of collagen colitis is 4-6 instances per 100,000 individuals. This condition is one of the reasons why older patients experience chronic diarrhea [2]. Collagen gastritis is linked to the deposition of collagen in the subepithelial layer of the stomach lining in pediatric practice, as per the findings of study by Timo Käppi et al. and Changqing Ma et al. [3, 4]. Although there have been reports of kid cases with separate collagen colitis and enteritis [5, 6], they are almost invariably associated with collagen gastritis.

It is noteworthy that a 12-year study of the case of collagen gastritis in a woman described by Colletti et al. revealed progressive atrophy of the glands, intestinal metaplasia, linear neuroendocrine hyperplasia and changes in the surface epithelium, interpreted as uncertain for dysplasia [7]. The study conducted a dynamic study of stomach mucosa bioptates (within 12 years) of a girl whose symptoms (epigastric pain, anemia, hemoptysis and hematohesy) first appeared at age 14. Histologically, subepithelial collagen bands up to 75 μm thick and inflammatory infiltrates in a large number of bioptates have been identified in the stomach lining since the onset of symptoms, confirming the diagnosis of "collagen gastritis". This evidence suggests that patients with collagen gastritis may have an increased risk of developing neuroendocrine stomach tumors and adenocarcinomas, but such cases have not yet been documented in the literature.

Many researchers consider CG as a chronic disease with a benign current. According to research Timo Käppi et al. There is insufficient evidence of CG pathogenesis and anemia as a clear reason for patients seeking treatment [3]. However, the severity of the anaemia, as well as possible relapses after the cessation of iron supplementation, represent a need to increase knowledge of pathology among physicians of all specialties, especially gastroenterologists.

Collagen gastritis is a rare gastrointestinal disease, first described in 1989 by Colletti et al. a 15-year-old girl with recurring abdominal pain and bleeding from the upper gastrointestinal tract [8]. This patient and five other cases were for the first time repelled by Colletti et al. in 1998, in its work [9], which aroused the particular interest of the scientific community in this issue. Analysis of scientific publications of foreign colleagues [3] from 1989 to 2020 revealed no more than 300 cases of observation of collagen gastritis, one third of which are children. The current literature on CG with infancy consists mainly of clinical case reports, except for the description of six patient sample series (sampling criterion — detection of collagen band more than 10 μm thick in the subepithelium of the stomach lining) and three histopathological studies with limited clinical information and follow-up data. It should be noted that knowledge about the evolution of clinical, endoscopic and histological features of the disease over time is scarce, and pathogenesis remains insufficiently studied.

From the etiological point of view, the most common causes of the development of chronic gastritis (such as toxic, allergic, eosinophilic gastritis, sarcoidosis, histiocytosis, ischemic gastritis, chronic granulomatosis, etc.) have not been detected in patients with collagen gastritis. Helicobacter pylori also does not appear to be a fundamental part of the pathogenesis, and the causative barricade did not improve collagen gastritis.

Studies by Hugh J. Freeman (2005) indicate that it is currently unclear which triggers may cause collagen deposition in the mucous membrane of the digestive tract, and whether this mechanism is a by-product or cause of symptoms. Pathophysiological mechanisms of increased collagen synthesis in gastric mucosa have not been described so far in scientific publications, but there are works in which there are suspected mechanisms of collagen deposition at collagen colitis, that, given the paucity of knowledge on whether collagen diseases of the digestive tract are a single spectrum of diseases, may be applicable to collagen gastroenteritis [10].

D.A. Stampfl and L.S. Friedman, in their work on the pathophysiology of collagen colitis [11] hypothesized that collagen synthesis by the pericryptal myophyblasts could be a likely explanation for collagen. In the same paper, it is postulated that the subepithelial strip of collagen in digestive tract collagen diseases consists of type III collagen with a reduced content of type I collagen. Type III collagen is produced by subepithelial fibroblasts to restore mucosa after inflammation. The basal membrane of the normal gastrointestinal tract consists of type IV collagen, indicating the fact of increased collagen synthesis not as a primary process, but rather reparative [10]. Other researchers have found that the collagen band at CC consists mainly of tenascine (glycoprotein extracellular matrix) and collagen type VI, as well as some type III collagen [12]. Tenascin is considered a marker of proliferation and migration of mesenchymal cells; therefore, the authors imply high flow of extracellular matrix with formation of immature, loosely interstitial collagen matrix [12]. Collagen filaments of type VI help to connect cells to the extracellular matrix [12], this may explain why the collagen band can both break down and simultaneously form on other parts of the mucous membrane. However, the expression of the glycoprotein of the extracellular matrix is transient and is often limited to embryonic development. In the embryo, the expression of tenascine occurs in certain areas, such as the nerve crest, and then in areas where skeletal tissue is formed. It is re-expressed in certain adult tissues during normal and pathological tissue remodeling, such as oncogenesis or wound healing. In this case it seems most likely that tenascin is present as part of the reparative process after tissue damage and inflammation, rather than playing any etiological role in the pathogenesis of collagen diseases of the digestive tract [12].

It should be noted that at present the pathophysiology of the disease is still not fully studied. Contrary to the above hypothesis, that increasing collagen synthesis in the mucous membrane of the digestive tract is not a primary process, but rather a postinflammatory reaction, a hypothesis was later put forward in research, subepithelial deposition of collagen and protein exudate occurs due to increased vascular permeability [13, 14].

Based on previously published reports on cases of the disease, two phenotypes of CC were described: "children" and "adult" [4]. It is not clear whether they are part of the same spectrum of pathology or not. In children, inflammatory changes and collagen deposition in the mucous membrane are usually limited to the stomach [3]. In contrast, adult form is associated with diffuse collagen lesions of the gastrointestinal tract, more often collagen colitis and other autoimmune disorders such as celiac disease or diabetes mellitus [3]. Collagen deposition and inflammatory infiltration in adults can be determined throughout the gastrointestinal tract. Gastrointestinal symptoms in adults include abdominal pain, abundant diarrhea without blood impurity in the stool, and the development of malabsorption syndrome with protein loss.

In 1998, Colletti et al. also reported the first "adult" phenotype observed in an 11-year-old boy [9]. Currently there are several cases of "adult" phenotype in pediatric patients [5, 9, 15]. Data are presented showing the occurrence of collagen gastritis in children in combination with collagen colitis. For example, in the comparative study Changqing Ma et al. 31 cases of collagen gastritis (10 cases in children and 21 cases in adults) were analyzed, their clinical, endoscopic, pathological and subsequent results were described. Both children and adults had similar clinical symptoms, such as anemia (50 and 35% respectively), epigastric/abdominal pain (50 and 45%) and diarrhea (40 and 55%). Associated immune disorders were found in 2 (20%) children and 3 (14%) adults [4]. It should be noted that histologically differences between children and adults with the manifestation of collagen gastritis are also not revealed: changes in the mucous membrane in the localization of stomach lesions, the mean thickness of the collagen layer and the amount of eosinophils were found to be equivalent in two study groups. Extragastric collagen lesions have also been observed with a comparable frequency in each cohort (44% and 59%). Follow-up information was available for 22 of 31 (71%) patients. In spite of the drug treatment, 100% of children and 82% of adults have retained their clinical histology. Thus, it has been proved that there are no significant clinical pathological differences between pediatric and adult patients with collagen gastritis [4].

DIAGNOSIS

According to the research Timo Käppi et al. Six out of 15 children (45%) reported recurrent abdominal pain at targeted collection, although in most cases the pain was not described as intense or affecting daily life. However, in the only

patient with associated collagen colitis, recurrent diarrhea dominated among the presented symptoms, despite supportive therapy. Other clinical manifestations also described: heartburn and/or dysphagia, nausea, constipation, bloating, insufficient weight gain, episodes of gastrointestinal bleeding, swelling, etc. In summary, the main complaint is often anemia (e.g., complaints of fatigue and pallor) combined with gastrointestinal symptoms, including iron deficiency anemia, which in some cases triggered a diagnostic examination, it was a random find discovered when patients sought medical attention. The etiology of anemia in CG is thought to be blood loss associated with damage to the dilated capillaries captured by the sub-epithelial collagen band. Timo Käppi Wolving and others. The study notes that in some cases the clinical and/or endoscopic signs of gastric bleeding in children with CG do not correlate with the severity of anemia, which often relapses against the backdrop of supporting iron therapy. The authors suggest that iron deficiency in these patients may be the result of reduced absorption of iron due to stomach hypochlorohydria or other mechanisms, and this issue requires further study [3].

Lee Yeoun Joo and others. Clinical cases describing the endoscopic picture of collagen gastritis in children, represented by characteristic nodulity and multiple polypoid growth against the background of pale mucosa, have been demonstrated. Compared to other associated stomach diseases, in which «nodules» are homogeneous in size and mainly located in the anthral department (eg, H. pylori-associated gastritis) the nodules at KG in most cases have a more irregular form and are located in the mucous membrane of the stomach body rather than the anthral department. Such changes in the stomach lining are often observed in general endoscopic procedures and are described as nodular or nodular gastritis (NG). It is therefore necessary to distinguish between the major diseases which may manifest in a similar way when a nodular pattern of the stomach lining is found in endoscopy. Endoscopic results of CG are reported to vary according to age: from normal mucous membrane to diffuse erythema of stomach mucous membrane, erosion, gastric hemorrhages, nodules and polyp's growth [16].

Histologically, nodules in nodular gastritis are more likely to be clusters of lymphoid follicles or malignant cells, for example in lymphoma associated with the stomach lining. Meanwhile, nodules at collagen gastritis are represented rather by a patch of mucous membrane with normal architectonics, surrounded by a "depressed" reparative atrophied mucosa with subepithelial collagen deposits, thus producing a characteristic nodular appearance. Based on available scientific data, the maximum thickness of subepithelial collagen deposits at the time of diagnosis varies between 15 and 100 μm. Furthermore, histologically, most patients have cell infiltration of the gastric mucosa with a high content of eosinophils (30 eosinophils/high power field). In contrast, intraepithelial lymphocytosis (>25 surface intraepithelial lymphocytes/100 epithelial cells) is much less common [3].

TREATMENT

Currently, there are no effective and standardized treatments for patients with collagen gastritis. For example, a wide range of drugs were used in the analysis of publications, including glucocorticosteroids (Budesonide), antimetabolites (Methotrexate), H_1-histamine blocks (Ranitidine), proton pump inhibitors (Omeprazole), a synthetic analogue of prostaglandin E1 (Misoprostol), gastroprotectors (Sucralfat), preparations of 5-aminosalytic acid (Mesalazine) [17, 18]. Of the non-medicamentous treatments, note the successful treatment of collagen gastritis in a 13-year-old boy on a gluten-free diet with a decrease in clinical symptoms after a month and resolution after 6 weeks from the start of treatment [19].

It is worth emphasizing that the analysis of the publications does not provide convincing data on the persistent improvement of the endoscopic and histological picture in the form of absorption or significant reduction of subepithelial collagen deposits even against the background of the therapy. Thus, the lack of expected effect on any particular intervention, other than the clinical improvement against the backdrop of iron supplementation presented in most publications, as well as reports of spontaneous clinical resolution of symptoms without medication raise the question of further search for adequate therapy of the disease, conducting randomized clinical trials to determine a scientifically based standard of treatment for the disease. Therefore, these patients now require dynamic surveillance, symptom control, especially anemia, testing for various autoimmune and immuno-mediated diseases. It seems necessary to control the endoscopic picture of the stomach mucous membrane, as one should not forget about the potential malignant hyperplasia of endocrine cells with the development of adenocarcinoma.

ADDITIONAL INFORMATION

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

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

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INTENSIVE CARE OF COMPLICATIONS OF DIABETES MELLITUS IN CHILDREN

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Abstract. *Introduction.* Complications of diabetes mellitus are one of the most common life-threatening conditions in pediatric practice. The *aim of the study* was to analyze modern principles of intensive therapy of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic coma (HHC) in children. *Results.* The peculiarities of volemic load and insulin therapy were demonstrated, special attention was paid to prevention and correction of intracranial hypertension, treatment of cerebral edema. The necessity of prevention of sharp fluctuations of blood plasma osmolarity, timely and step-by-step correction of water-electrolyte disorders was noted. *Conclusion.* The basis of successful treatment of diabetes mellitus complications in children is early diagnosis and correction of systemic hypoperfusion, prevention of cerebral ischemia and intracranial hypertension.

Key words: *type 1 diabetes mellitus; complications; children; diabetic ketoacidosis; intensive therapy.*

ИНТЕНСИВНАЯ ТЕРАПИЯ ОСЛОЖНЕНИЙ САХАРНОГО ДИАБЕТА У ДЕТЕЙ

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Резюме. *Введение.* Осложнения сахарного диабета являются одними из наиболее распространенных жизнеугрожающих состояний в педиатрической практике. *Цель исследования* — анализ современных прин-

ципов интенсивной терапии диабетического кетоацидоза (ДКА) и гиперосмолярной гипергликемической комы (ГГК) у детей. *Результаты.* Продемонстрированы особенности волемической нагрузки и инсулинотерапии, особое внимание уделено профилактике и коррекции внутричерепной гипертензии, лечению отека головного мозга. Отмечена необходимость предотвращения резких колебаний осмолярности плазмы крови, своевременной и поэтапной коррекции водно-электролитных нарушений. *Заключение.* Основой успешного лечения осложнений сахарного диабета у детей является ранняя диагностика и коррекция системной гипоперфузии, предотвращение церебральной ишемии и внутричерепной гипертензии.

Ключевые слова: *сахарный диабет 1-го типа; осложнения; дети; диабетический кетоацидоз; интенсивная терапия.*

INTRODUCTION

Diabetes mellitus (DM) is one of the most severe systemic diseases of childhood with extremely high risk of developing life-threatening conditions. The diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic coma, and hypoglycemia are the most dangerous of these disorders, because all of them can lead to severe neurological deficits [1, 2].

The incidence of diabetic ketoacidosis (DKA) is 1–10% per year in children with type 1 diabetes mellitus in developed countries with adequate health care resources, and it is the first manifestation of diabetes mellitus in approximately 30% of patients [3]. The risk of DKA is the highest in children of first two years of life and in adolescent girls, especially from socially disadvantaged families [4]. The high probability of diabetic ketoacidosis in early-age patients is possible due to an insufficient caution and late diagnosis of diabetes. At the same time, the main cause of diabetes decompensation in adolescents is a low adherence to treatment [4, 5].

The diabetic ketoacidosis (DKA) is the most common cause of death in children with DM, its incidence is 2–5%. An irreversible damage of central nervous system (CNS) in children with DKA is a consequence of cerebral edema. The risk of the condition is about 1–1.2%, and mortality rates with refractory intracranial hypertension are 20–25% [6]. A severe neurologic deficit is observed in more than 35% of surviving patients.

The most common reason for the onset of cerebral edema is severe metabolic disorder, which has a damage effect to the main metabolic pathways. At the same time, in some cases the progression of intracranial hypertension has a clear relationship with the peculiarities of the therapy, which can be quite aggressive and after a while become the cause of patient deterioration [1, 2, 4–6].

The rarest complications of DKA include acute respiratory distress syndrome, rhabdomyolysis, and acute renal failure.

K. Lah Tomulić et al (2022) had evaluated the epidemiology of DKA in patients of intensive care unit (ICU) over the last 10 years and demonstrated that ketoacidosis as the first manifestation of type 1 DM was in 24.7% of children. A moderate and severe dehydration was noted in 76% on admission, 5.2% of patients developed cerebral edema, one child died [7].

All these facts show the relevance and clinical significance of the problem, because timely diagnosis and adequate intensive therapy of complications of DM in children will significantly improve results of treatment and outcome of the disease.

The diabetic ketoacidosis is an acute diabetic decompensation of metabolism, manifested by a sharp increase in the concentration of glucose and ketone bodies in the blood, their appearance in the urine and development of a metabolic acidosis. It can be leaded with varying states of impaired consciousness or without them, which requires emergency hospitalization of the patient [4].

Due to international and domestic clinical guidelines, the criteria for the diagnosis of DKA in children are blood glucose concentration > 11 mmol/L, blood pH below 7.30, bicarbonate (HCO_3) concentration less than 15 mmol/L, increased anion gap, and ketosis (blood β-hydroxybutyrate concentration > 3 mmol/L) or ketonuria (moderate or severe). The symptoms of clinical manifestation of DKA are a weakness, nausea, vomiting, abdominal pain, polydipsia, polyuria, polyphagia, depression of consciousness, Kussmaul's breathing, and acetone odor from the mouth. Three stages are distinguished, depending on the severity of the clinical picture of DKA (Table 1).

Table 1. Degrees of severity of diabetic ketoacidosis

Таблица 1. Степени тяжести диабетического кетоацидоза

Клинические рекомендации Российской Федерации / Clinical Recommendations of the Russian Federation		
Степень тяжести / Degree of severity	pH	HCO_3, ммоль/л / HCO_3, mmol/l
Легкая / Mild	<7,3	<15
Средняя / Moderate	<7,2	<10
Тяжелая / Severe	<7,1	<5

Педиатрия по Нельсону / Nelson Textbook of Pediatrics			
Степень тяжести / Degree of severity	pH	pCO_2, мэкв/л / pCO_2, mEq/l	Клинические признаки / Clinical signs
Легкая / Mild	7,25–7,35	16–20	Пациент ориентирован, может быть возбужденным или вялым / Orient, alert but fatigued
Средняя / Moderate	7,15–7,25	10–15	Дыхание Куссмауля, пациент сонлив, но приходит в ясное сознание при стимуляции / Kussmaul respiration, oriented but sleepy, arousable
Тяжелая / Severe	<7,15	<10	Дыхание Куссмауля или брадипноэ, угнетение сознания вплоть до комы / Kussmaul or depression respirations, sleepy to depressed sensorium to coma

Table 2. Differential diagnosis of diabetic ketoacidosis and hyperosmolar hyperglycemic coma

Таблица 2. Дифференциальная диагностика диабетического кетоацидоза и гиперосмолярной гипергликемической комы

Лабораторные критерии / Laboratory criteria	Диабетический кетоацидоз / Diabetic ketoacidosis	Гиперосмолярная кома / Hyperosmolar hyperglycemic coma
Концентрация глюкозы в крови, ммоль/л / Glucose, mmol/l	>13,9	33,3
pH артериальной крови / pH arterial blood	<7,3	>7,3
Бикарбонат, ммоль/л / Bicarbonate, mmol/l	<15	>15
Осмолярность, мОсм/кг / Osmolarity, mOsm/kg	<320	>330
Кетонурия / Ketonuria	+++	±
Анионный градиент / Anion gap	>12	<12

A differential diagnosis of DKA should be done with hyperosmolar hyperglycemic nonketotic coma occurring in type 2 diabetes, although it is extremely rare in children (Table 2).

PECULIARITIES OF INTENSIVE THERAPY OF DIABETIC KETOACIDOSIS

The intensive therapy of diabetic ketoacidosis includes mandatory components: elimination of the phenomena of shock if it is presented, step-by-step correction of dehydration and electrolyte disorders, management of ketoacidosis and hyperglycemia, prevention and treatment of cerebral edema. For this purpose, an infusion and insulin therapy is used. The algorithm of intensive therapy of DKA, taking into account the available recommendations, is presented in figure 1. If a heart rate and blood pressure are stable, the infusion therapy should be started, including fluid supplementation (maintenance requirements and compensation of the deficit taking into account current pathologic losses). The degree of dehydration is based on the clinical and laboratory examination. Main characteristics are presented in Table 3.

The approximate fluid administration and electrolyte requirements are demonstrated in Table 4.

The first-line infusion is NaCl solution or any balanced polyionic solution in the absence of clinically significant hyperkalemia. The choice of the concentration of the NaCl solution (0.9%

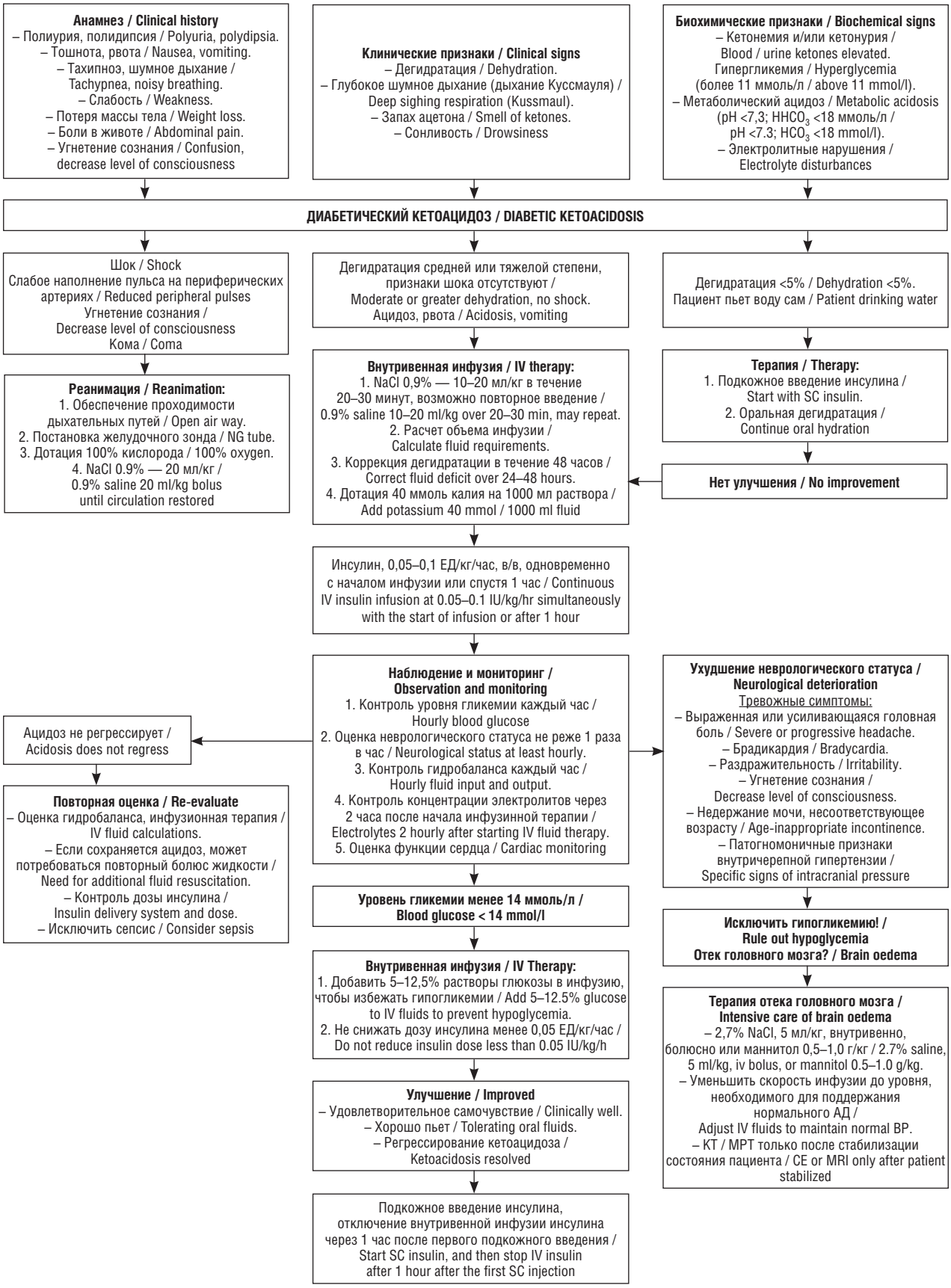

Fig. 1. Algorithm of intensive care of diabetic ketoacidosis in children

Рис. 1. Алгоритм интенсивной терапии диабетического кетоацидоза у детей

or 0.45%) depends on the concentration of sodium in the plasma. In case of the normonatremia, 0.9% solution is used, and in hypernatremia (Na+ > 150 mmol/L) — 0.45% solution. Although, the use of its appointment is not recognized by all authors. In case of the hyponatremia, the plasma sodium concentration should be calculated due to the level of glycemia:

$$[Na^+] = [Na^+] + \frac{[\text{blood glucose}] - 5{,}6}{5{,}6} \cdot 1{,}6.$$

The use of hypertonic solutions for hyponatremia in patients with DKA is categorically contraindicated! The drug of choice in this situation is 0.9% NaCl solution.

When glucose concentration decreases by 1 mmol/L, the plasma sodium concentration should be increased by 1.6 mmol. **The decrease sodium concentration in dynamics against hyperglycemia is a sign of progression of cerebral edema!**

A fluid deficiency should be compensated for at least 24–36 hours, and if there is a high risk of cerebral edema — 48 hours. The faster elimination of dehydration can cause a sharp decrease in plasma osmolarity and progression of an intracranial hypertension. The rate of decrease in plasma osmolarity should not exceed 1.5–2.0 mOsm/hour.

A necessary component of the infusion program is the donation of potassium in order to eliminate its deficiency and prevent the development of cardiac arrhythmias (Table 4).

The potassium treatment is prescribed only after elimination of pronounced manifestations of a hypovolemia, in the presence of adequate diuresis and serum K+ concentration less than 5.0 mmol/L [9]. It should be noted that in DKA the need for potassium is at least 150% of the age requirement: 1.5–3.0 mEq/kg per day.

In case of normokalemia (4-6 mmol/L) the potassium is administered at the rate of 40 mEq in 1L of infusion solution, and in hypokalemia — 60 mEq/L.

In case of severe hypokalemia (blood potassium concentration less than 3.0 mmol/L), potassium solutions are administered in dose of 0.5 mmol/kg per hour for one hour with subsequent assessment of potassium levels in blood.

When the blood glucose concentration drops to 14-17 mmol/L, a 5 or 10% glucose solutions should be added to the infusion on the background of insulin therapy, and it is better to use the concept of "two packets". So, each of these bags contains the same amount of electrolytes, but only one of them is added glucose. The technique allows faster, more economical and accurate correction of the dose of administered glucose, which is titrated due to its concentration in the blood. This approach can pre-

Table 3. Assessing the severity of dehydration in children with diabetic ketoacidosis

Таблица 3. Оценка степени тяжести дегидратации у детей с диабетическим кетоацидозом

Степень тяжести / Degree of severity	Степень дегидратации / Degree of dehydration
Легкая, средняя степень / Mild, moderate	5% от массы тела / 5% of body weight
Тяжелая / Severe	10% от массы тела / 10% of body weight

Table 4. Fluid and electrolyte requirements in diabetic ketoacidosis [5]

Таблица 4. Потребность в жидкости и электролитах при диабетическом кетоацидозе [5]

Компонент / Component	Потери при ДКА, ЕД/кг / Average (range) losses per kg	Возрастная суточная потребность / 24-hour maintenance requirements	
Вода / Water	70 (30–100) мл/ml	<10 кг / kg	100 мл/кг / 100 ml/kg
		11–20 кг / kg	1000 мл + 50 мл/кг на каждый кг после 10 кг веса / 1000 ml + 50 ml/kg/24 h for each kg from 11 to 20
		>20 кг / kg	1500 мл + 20 мл/кг на каждый кг после 20 кг веса / 1500 ml + 20 ml/kg/24 h for each kg >20
Натрий / Sodium	6 (5–13) ммоль / mmol	2–4 ммоль / mmol	
Калий / Potassium	5 (3–6) ммоль / mmol	2–3 ммоль / mmol	
Хлор / Chloride	4 (3 – 9) ммоль / mmol	2–3 ммоль / mmol	
Фосфор / Phosphate	0,5–2,5 ммоль / mmol	1–2 ммоль / mmol	

vent the hypoglycemia despite the constant need for insulin [10].

Both insufficient and excessive fluid administration can cause a significant increase or decrease in blood plasma osmolarity and progression of intracranial hypertension [4, 5, 11].

Against the background of circulating blood volume recovery and stabilization of hemodynamic parameters, insulin therapy at a starting dose of 0.05-0.1 U/kg per hour until regression of ketoacidosis is mandatory [5, 12, 13]. The insulin is prescribed immediately after administration of a fluid bolus or at the same time with the start of infusion therapy. In patients with DKA, only short-acting insulin preparations (Novorapid, Actrapid NM, etc.) should be used. The pharmacokinetics of short-acting insulins is presented in Table 5.

Until a ketoacidosis regression, an insulin dose of less than 0.05 units/kg per hour should not be used. The optimal blood glucose level should be maintained by infusion of 5 or 10% glucose solutions.

The main objective in the treatment of patients with DKA is not to eliminate hyperglycemia, but to eliminate the signs of ketoacidosis [11].

An intravenous and subcutaneous bolus injection of insulin is absolutely contraindicated in DKA. The dose of insulin and the rate of infusion of solutions for infusion therapy are selected so that the rate of decline of blood glucose does not exceed 5.0 mmol/L per hour, although the optimal rate of decline is 2 mmol/L per hour. If there is no effect of insulin therapy within two hours, the insulin dose can be increased to 0.15 IU/kg per hour, but this is a last resort way that can only be used as an exception to the rule.

After a complete elimination of ketoacidosis signs, a child should be examined by an endocrinologist to decide a possibility to change IV infusion of insulin to subcutaneous injections.

During infusion and insulin therapy, sharp spikes in blood glucose levels and a hypoglycemia should be avoided, because both a significant decrease and increase in blood plasma osmolarity can cause progression of intracranial hypertension [4, 5, 11].

Against the background of fluid and insulin administration, a significant decrease in blood plasma osmolarity can be observed with its simultaneous increase within the cellular structures of the CNS. This is the one of the factors that can lead to or aggravate an already existing cerebral edema [11].

Table 5. Pharmacokinetics of short-acting insulins

Таблица 5. Фармакокинетика инсулинов короткого действия

Характеристика / Characterization	Описание / Description
Начало действия / Start of action	Через 20–30 минут от начала инфузии / After 20–30 minutes from the beginning of infusion
Максимум действия / Maximum action	Через 2,5–3,5 часа / After 2.5–3.5 hours
Продолжительность действия / Duration of action	6–8 часов / 6–8 hours

A rapid decrease in plasma glucose concentration may also contribute to the development of cerebral edema in patients with DKA. In particular, it may cause a decrease in plasma osmolarity and fluid movement into the CNS structures; therefore, glucose levels of plasma should be kept in the range of 8–12 mmol/L [4, 5, 11].

The most controversial issue of intensive therapy of diabetic ketoacidosis is the use of sodium bicarbonate solution to correct metabolic acidosis [4–6].

According to many authors, the use of a sodium bicarbonate is the main risk factor for the cerebral edema in DKA. They think, that against the background of infusion of sodium bicarbonate solution, secondary hypoxemia of CNS neurons develops due to the shift of oxyhemoglobin dissociation curve [6].

Both in acidosis and alkalosis there is a shift of the oxyhemoglobin dissociation graph. There is a shift to the left in alkalosis characterized by an increase in the affinity of hemoglobin to oxygen. The hemoglobin is quickly saturated with oxygen in the lungs and very slow gives it to tissues. It is always an unfavorable sign and indication a marked disturbance of oxygenation. Even an increase in blood oxygen content does not improve tissue oxygenation, which should be noticed when there are a cerebral edema and performing artificial respiration. Several studies demonstrate that the use of sodium bicarbonate is accompanied by paradoxical acidosis of cerebrospinal fluid, which was the basis for the negative attitude of different researchers to the use of sodium bicarbonate in patients with DKA [6]. The sodium bicarbonate is extremely harmful in patients with diabetic ketoacidosis and can be used

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only if there is a high probability of myocardial depression on the background of metabolic acidosis [2, 6, 11, 14, 15].

The ketoacidosis gradually regresses with adequate infusion and insulin therapy in the majority of clinical cases. But sometimes the decompensated metabolic acidosis may persist and sodium bicarbonate (0.5–1.0 mEq/kg for 30–60 minutes) can be appropriate. Both we and other authors believe that the use of sodium bicarbonate can be justified only in the presence of decompensated metabolic acidosis (pH < 7.1) and a high risk of acute myocardial depression [11, 14, 15]. There is a small experience of correction of metabolic acidosis and hyperglycemia in children with DKA using infusion solutions containing succinate [16].

In some cases, even while an adequate infusion and insulin therapy, progression of intracranial hypertension and clinical symptoms of cerebral edema are noted. Its diagnostic criteria are presented in Table 6. The necessary components of therapy are restriction of the volume of fluid, using of osmotic diuretics, tracheal intubation and transfer the patient to invasive mechanical ventilation in case of progression of cerebral edema in patients with DKA [4, 5, 11]. If the patient has depressed consciousness without obvious clinical signs of progression of intracranial hypertension and consciousness of the level of coma, use of osmotic diuretics is categorically contraindicated.

An artificial ventilation should be used only if it is a last way and there is a decompensated respiratory failure and high risk of aspiration syndrome. It is important to note that severe hypocapnia is a risk factor for the progression of cerebral edema, because low levels of carbon dioxide tension in the blood lead to a cerebral vasospasm, impaired autoregulation of cerebral blood flow and ischemia in CNS [17].

In patients with DKA it is advisable to maintain the level of pCO_2 as it was before tracheal intubation, avoiding excessive decrease and increase of pCO_2, because the hypocapnia is a compensatory mechanism aimed at eliminating ketoacidosis [11].

Drugs of choice for correction of intracranial hypertension are mannitol and/or hypertonic sodium chloride. The intravenous drip mannitol is administered at a dose of 0.5–1.0 g/kg for 20 minutes. If there is no effect, it can be done again. While using mannitol, improvement of cerebral blood flow and cerebral oxygenation is noted.

A hypertonic sodium chloride (3%) is used drip intravenously at a dose of 5-10 ml/kg for 30 minutes. The main advantage of hypertonic sodium chloride compared with mannitol is the prevention of hyponatremia and hypovolemia while there is an osmotic diuresis [3]. It can be used as a "second-line" drug in the absence of effect from mannitol.

Table 6. Criteria for the diagnosis of cerebral edema in patients with diabetic ketoacidosis [11]

Таблица 6. Критерии диагностики отека мозга у пациентов с диабетическим кетоацидозом [11]

Диагностические критерии / Diagnostic criteria	«Большие» критерии / "Major" criteria	«Малые» критерии / "Minor" criteria
1. Неадекватная двигательная или вербальная реакция в ответ на болевой раздражитель / Abnormal motor or verbal response to pain. 2. Декортикационная или децеребрационная ригидность / Decorticate or decerebrate posture. 3. Паралич черепно-мозговых нервов (особенно III, IV и VI) / Cranial nerve palsy (especially III, IV, VI). 4. Наличие патологических типов дыхания (дыхание по типу «гасп», тахипноэ, дыхание Чейна–Стокса, апноэ) / Abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne–Stokes, apneustic)	1. Угнетение или ундулирующее сознание / Altered mentation or fluctuating level of consciousness. 2. Уменьшение частоты сердечных сокращений (более чем на 20 в минуту), не связанное со сном или стабилизацией показателей гемодинамики / Sustained heart rate deceleration (decline more than 20 per minute) not attributable to improved intravascular volume or sleep state. 3. Несоответствующее возрасту возбуждение / Age-inappropriate incontinence	1. Рвота / Vomiting. 2. Головная боль / Headache. 3. Диастолическое артериальное давление более 90 мм рт.ст. / Diastolic blood pressure greater than 90 mm Hg. 4. Возраст менее 5 лет / Age <5 years

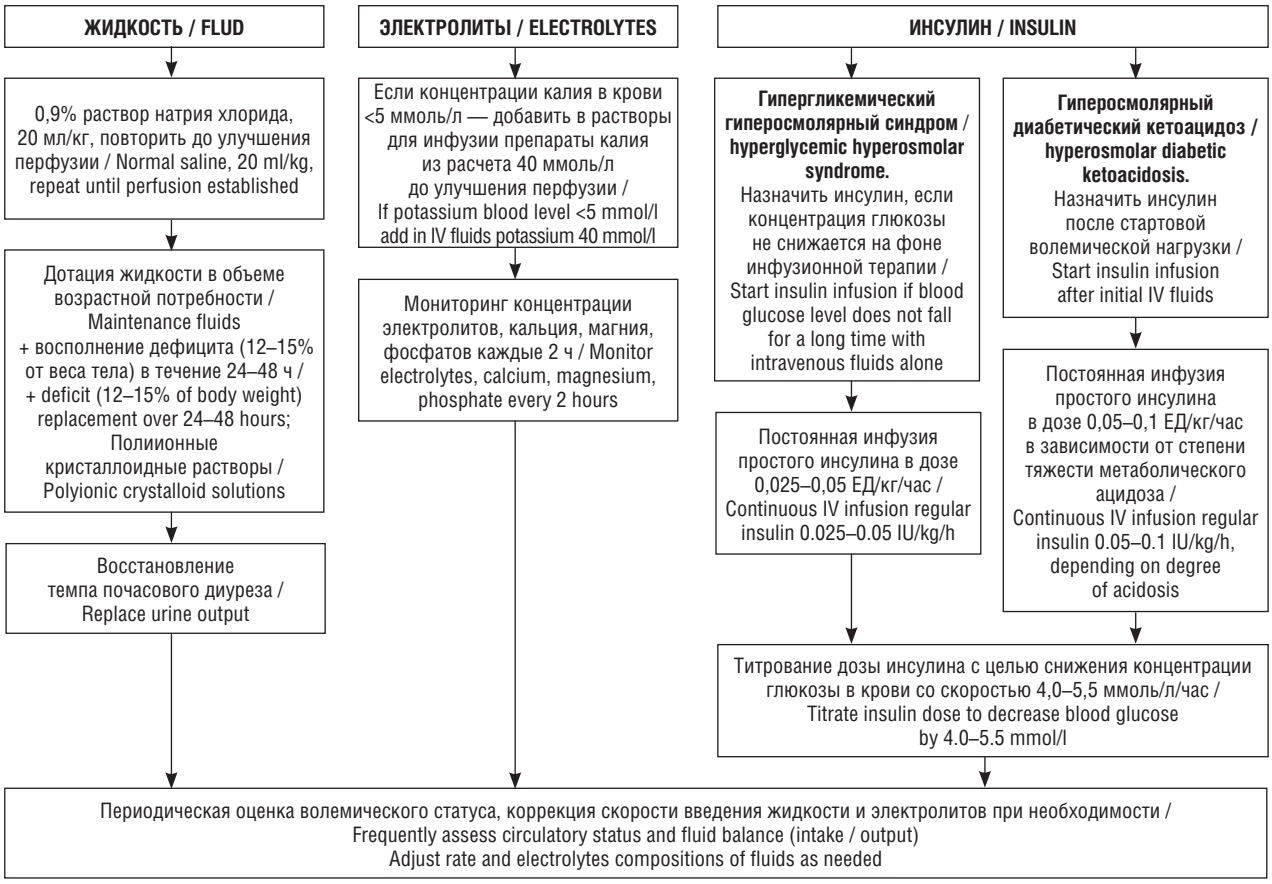

Fig. 2. Algorithm of intensive care of hyperosmolar hyperglycemic coma

Fig. 2. Algorithm of intensive care of hyperosmolar hyperglycemic coma

PECULIARITIES OF INTENSIVE CARE OF HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC COMA

The main distinguishing feature of treatment of hyperosmolar hyperglycemic nonketonic coma is the correction of water and electrolyte disorders. The use of insulin preparations is justified if the blood glucose level does not decrease while the patient is giving an infusion therapy. The starting dose of insulin should not exceed 0.05 U/kg per hour (Fig. 2).

CONCLUSION

At the end of the review of modern principles of intensive care of complications in children with diabetes mellitus, it should be noted that any rash and routine intervention can bring both benefit and harm. Thus, cautious and timely assessment of the patient's condition and subsequent correction of therapy are necessary.

ADDITIONAL INFORMATION

Author contribution. Concept and design of the study: Aleksandrovich Yu.S., Pshenisnov K.V.; collection and processing of primary material: Pshenisnov K.V., Muratov P.A., Ditkovskaya L.V.; writing the text of the article: Pshenisnov K.V., Prometnoy D.V., Kopylov V.V., Muratov P.A.; editing: Ivanov D.O., Aleksandrovich Yu.S. All authors read and approved the final version before publication.

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ASSESSMENT OF SCHOOL MATURITY OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY SYNDROME

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Abstract. Nowadays, one of the necessary tasks of a pediatrician is to assess the child's readiness for the schooling. The process of a child's transition from kindergarten to school is a real test, because in addition to the academic load that children are given from the first days of school, they need to go through a period of adaptation and socialization among their peers. Children with diseases of the nervous system, including attention deficit hyperactivity disorder, may be immature by the time they enter school, which will subsequently lead to poor academic performance, maladjustment and conflicts with peers and teachers due to a decrease in adaptive and communication abilities.35 children of senior preschool age (17 girls, 18 boys) from the city of Veliky Novgorod took part in the study. To assess school maturity, the Kern–Jirasik test was used. ADHD was more often reported in boys. In 36% of cases, children with ADHD had neurological features in the form of delayed speech development, 12% had local tics, and 16% had enuresis. The study found that 60% of children with attention deficit hyperactivity disorder had a low level of school maturity, while 50% of children in the control group had a high level of school maturity.When studying personal maturity, fine motor skills and visual coordination, visual-spatial perception and visual memory, as well as intellectual maturity, a low level of development prevailed in children with attention deficit disorder, while a high level of these indicators predominated in healthy children. Children with attention deficit hyperactivity disorder are not ready for school; this requires further development of approaches to teaching such children.

Key words: *attention deficit hyperactivity disorder; Kern and Jirasik test; school readiness assessment.*

ОЦЕНКА ШКОЛЬНОЙ ЗРЕЛОСТИ ДЕТЕЙ, ИМЕЮЩИХ СИНДРОМ ДЕФИЦИТА ВНИМАНИЯ И ГИПЕРАКТИВНОСТИ

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Резюме. В наше время одной из необходимых задач врача-педиатра становится оценка готовности ребенка к обучению в школе. Процесс перехода ребенка из детского сада в школу является настоящим испытанием, потому что помимо учебной нагрузки, которая предоставляется детям с первых дней школы, им необходимо пройти период адаптации и социализации среди сверстников. Дети с заболеваниями нервной системы, в том числе и с синдромом дефицита внимания и гиперактивности (СДВГ), могут оказаться незрелыми к моменту поступления в школу, что в последующем повлечет за собой плохую успеваемость, дезадаптацию и конфликты со сверстниками и учителями из-за снижения адаптационных и коммуникатив-

ных способностей. В исследовании приняли участие 35 детей старшего дошкольного возраста (17 девочек, 18 мальчиков) города Великий Новгород. Для оценки школьной зрелости был использован тест Керна–Йирасика. СДВГ чаще регистрировался у мальчиков. В 36% случаев дети с СДВГ имели неврологические особенности в виде задержки речевого развития, 12% — локальные тики, 16% — энурез. В ходе исследования было установлено, что 60% детей с синдромом дефицита внимания и гиперактивности обладали низким уровнем зрелости, в то время как 50% детей в контрольной группе имели высокий уровень школьной зрелости. При исследовании личностной зрелости, мелкой моторики и зрительной координации, зрительно-пространственного восприятия и зрительной памяти, а также интеллектуальной зрелости у детей с синдромом дефицита внимания преобладал низкий уровень развития, у здоровых детей наблюдалось преобладание высокого уровня данных показателей. Дети, имеющие СДВГ, не готовы к школьному обучению, это требует дальнейшей разработки подходов к обучению таких детей.

Ключевые слова: *синдром дефицита внимания и гиперактивности; тест Керна и Йирасика; оценка готовности к школе.*

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a behavioral developmental disorder characterized by impaired control, decreased attentiveness, high levels of impulsivity and motor activity [1]. This mental disorder is diagnosed in 8–15% of cases in pediatric practice all over the world, and in 60% of cases the disorder persists into adulthood [2]. In European countries, the ratio of ADHD occurrence in boys and girls ranges from 3:1 to 16:1 [3]. The incidence of the disease has increased very much over the last 20 years, from 2.2 to 30% as well as the prevalence of autism.

Nowadays, the exact etiology is unclear, but some studies link the pathology to genetic predisposition and central nervous system damage at the early stages of development [4]. Psychoemotional stress may also be the cause of ADHD [5].

There are three types of ADHD: hyperactive/impulsive type, inattentive type, and combined type [6].

The problem of ADHD is poorly studied in children. Nowadays, insufficient awareness of the disease among both teachers and parents leads to the decrease in the child's mental state. It also will affect his or her personality, self-esteem and socialization in the future [7]. In addition to the academic load that a child receives at the 1st grade of school, a student with ADHD has an enormous stress while adapting to new conditions and new society.

Children with ADHD have less adaptive and communicative abilities compared to their peers. Due to their immaturity by the time they enter school, children with ADHD have not only difficulties in understanding the school curriculum, but also problems with socialization. It can be manifested by conflicts with classmates and teachers [8]. These problems can affect the emotional state of the child in the future.

A number of authors have described the pathogenesis of the ADHD — the theory of impaired neurotransmitters metabolism that control the higher mental functions. It is a cause of the presence of additional neuropsychiatric disorders in children with ADHD [9].

THE AIM OF THE STUDY

The aim of the study is to assess the level of school readiness in children with attention deficit hyperactivity disorder.

MATERIALS AND METHODS

Thirty-five children of preschool age were examined in the city of Veliky Novgorod. The group of children with attention deficit hyperactivity disorder consisted of 25 children. No one has acute diseases at the time of the study. The control group consisted of 10 children. No one of them has acute and chronic diseases at the time of the study too. The Kern-Jirasek test [10] was used to determine school maturity. All children underwent an anthropometry.

The first task was to draw a male figure. The presence of elements of male clothing, all facial components, and the number of fingers drawn on the limbs were important. This task assessed the child's personal maturity.

The second task was to write the proposed phrase. An attention was paid to the legibility of the written letters, their size, and the presence or absence of deviation of inscription from the horizontal level. This task was used to assess fine motor skills and hand-eye coordination.

The third task was to draw a group of ten dots. The number of dots, their size and deviation from

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the column or other dots were important. This task was used to assess visual-spatial perception and visual memory.

These three tasks were evaluated with a scale from 1 to 5, where 1 is a perfectly completed task and 5 is a major deviation of the task.

After assessing each of them, the scores were summed and the level of overall school readiness were determined.

The fourth task was a questionnaire (20 questions). Each answer of a question was converted to an equivalent point. After the addition of scores, the level of verbal intelligence was determined.

RESULTS

17 girls and 18 boys were in the study. The ADHD was registered more often in boys. The manifestation of ADHD occurred from 4th year of life, anamnesis vitae was without peculiarities. Children received at least 4 courses of symptomatic treatment (nootropics, adreno- and sympathomimetics, and vitamin therapy). All children attended kindergarten, where were additional lessons with a speech therapist and a psychologist. Children with ADHD visited a neurologist every 3 months. 50% of children were from large families or without sibs. An organic brain pathology was present in 40% of children. It can be cause of the lack of effectiveness of drugs and lessons with speech therapist and psychologist. The physical development of children in both groups was comparable to the normal.

Children with ADHD in 36% of cases had neurological features in the form of delayed speech development, 12% — local tics, 16% — enuresis (Fig. 1).

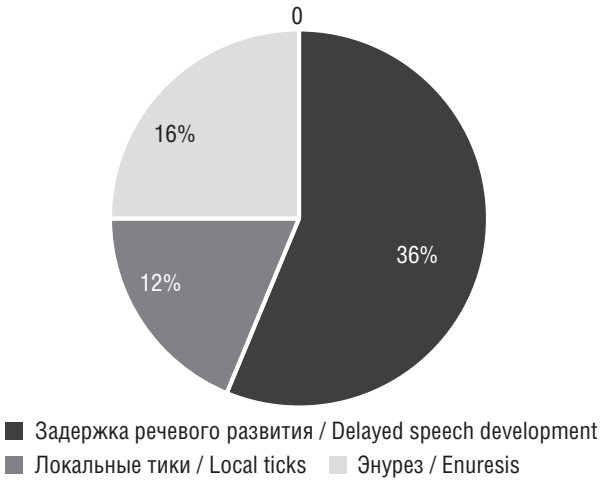

Fig. 1. Neurological characteristics of children with attention deficit disorder

Рис. 1. Неврологические особенности детей с синдромом дефицита внимания

The study found that 60% of children with ADHD had a low level of maturity, while 50% of children in the control group had a high level of school maturity.

We also have studied the personal maturity in children with attention deficit disorder. The low level of development prevails in this group (52% — low level, 20% — medium level, 28% — high level), in control group the high level prevails (60% — high level, 30% — medium level, 10% — low level). We observe a decrease in the level of personal maturity in the majority of children with ADHD compared to healthy children. This indicator can explain the inability of children with ADHD to independently predict their behavior, including motor activity, as well as an inability to adequate reacting to different situations. These qualities may affect the concentration of attention during the learning process, as well as the lack of motivation to fulfill the school plan.

The examination of fine motor skills and visual coordination detected that the low level was in children with ADHD (40% — low level, 32% — medium level, 28% — high level), and the high level was in healthy children (100% — high level). In this case, the presence of a lower level of development of fine motor skills and visual coordination in children with ADHD can lead to difficulties in writing and reading. Also it should be noted that in healthy children this task was performed at the highest level in 100% of cases. More than a half of children with ADHD performed this task at a high and average level.

In the study of visual-spatial perception and visual memory the low level of development prevails in children with ADHD (52% — low level, 20% — medium level, 28% — high level), and the high level prevails in second group (90% — high level, 10% — medium level). This result shows a pattern between children with ADHD and possible impairment of visual memory and visual-spatial perception, which can also be one of the causes of school failure.

The examination of intellectual maturity shows its low level in children with ADHD (36% — low level, 28% — below average level, 36% — average level), and the ratio of children with average and high level is 50% each in group 2.

The results show that children with ADHD are not ready for quick and well processing information, also they do not have an enough vocabulary

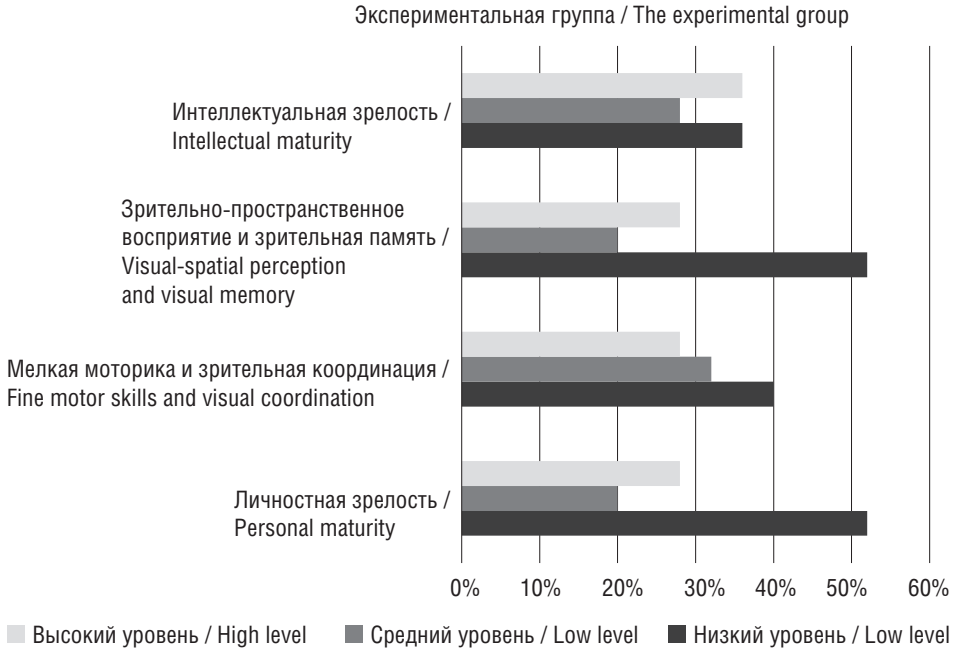

Fig. 2. Evaluation of the results of the Kern–Jirasik school maturity test in children with attention deficithy peractivity disorder

Рис. 2. Оценка результатов теста школьной зрелости Керна–Йирасика у детей с синдромом дефицита внимания и гиперактивности

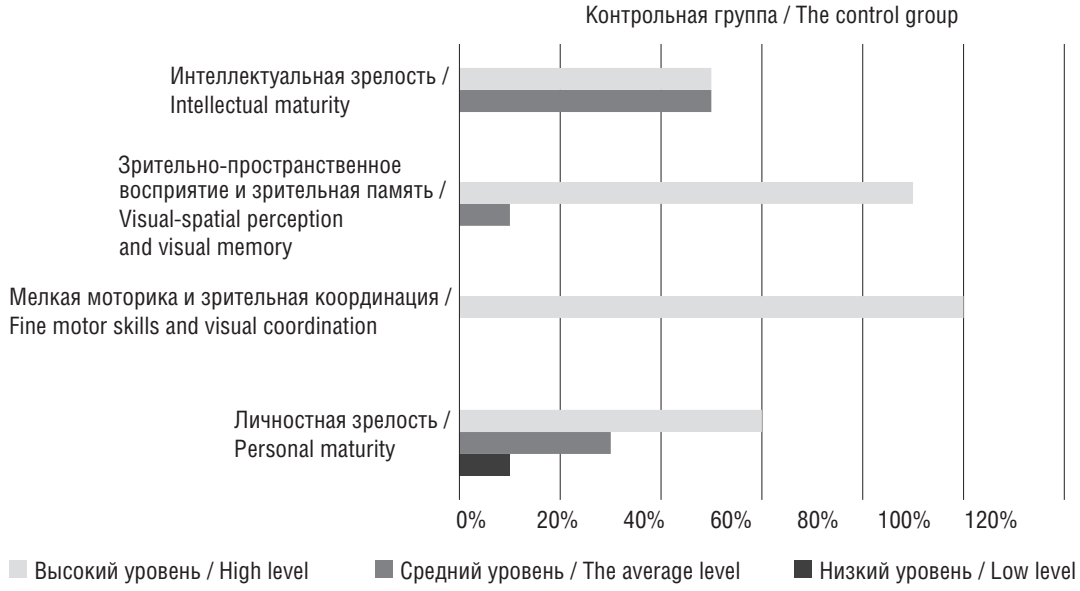

Fig. 3. Evaluation of the results of the Kern-Jirasik school test in healthy children

Рис.3. Оценка результатов теста школьной зрелости Керна–Йирасика у здоровых детей

or they are inability to apply it fully. In most cases, children with ADHD have a significantly lower level of verbal intelligence compared to healthy children (Fig. 2, 3).

CONCLUSIONS

Thus, children with ADHD have predominantly low levels of personal maturity, fine motor skills and hand-eye coordination, visual-spatial perception and visual memory, and also low levels of verbal intelligence. These markers are very important for studding and adaptation to school and new community.

1. Children with ADHD are not ready for schooling due to their immaturity, low personal maturity (52% — low level), fine motor skills and hand-eye

coordination (40% — low level), visual-spatial perception and visual memory (52% — low level), insufficient verbal intelligence compared to healthy peers (36% — low level).

2. The solution of the unpreparedness of children with ADHD for school are later first grade enrollment, attendance of pre-school lessons for better adaptation to new environment, classes with a speech therapist and psychologist, and individual approach of parents and pediatrician to the diagnostics and treatment.

We recommend an active sports and walking outside for the correct ratio of physical and mental activity. Individual lessons should be carried out with breaks, so the child does not have time to get tired. It is acceptable to use a game format while teaching immature children.

ADDITIONAL INFORMATION

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

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

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Consent for publication. Written consent was obtained from 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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ANALYSIS OF THE QUALITY OF LIFE OF PATIENTS AFTER SURGICAL OPERATIONS IN TERMS OF THE RISK OF DEVELOPING ADHESIVE INTESTINAL OBSTRUCTION

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Abstract. Numerous experimental, clinical and laboratory studies have been devoted to the prevention of postoperative adhesions. Taking into account the etiological factors and mechanisms of formation of postoperative adhesions, a wide variety of methods have been proposed to prevent them. We analyzed the long-term results of surgical interventions on abdominal organs in 317 patients who were followed up to 18 months. The main group consisted of 101 patients in whom the drug Hemoben was used intraoperatively to prevent adhesions. The comparison group included 216 patients who underwent interventions without the use of any anti-adhesive agents. In the long-term period (from 3 to 18 months) after surgery, 116 patients of the comparison group and 64 patients of the main group had their quality of life assessed using the GIQLI questionnaire (Gastrointestinal Quality of Life Index) specially designed for such a cohort of patients. The study of the subjective factor of assessing anti-adhesive effectiveness based on a comparative analysis of the quality of life level according to the GIQLI questionnaire showed a higher value of this indicator in the main group for all major domains, with a total score of 103.8 ± 9.8 versus 92.6 ± 10.8 points ($t = 7.12$; $p < 0.05$) (the indicator in the group of healthy individuals was 123.6 ± 5.1 points).

Key words: *adhesive intestinal obstruction; anti-adhesive agents; quality of life; Hemoben drug.*

АНАЛИЗ КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ ПОСЛЕ ХИРУРГИЧЕСКИХ ОПЕРАЦИЙ В АСПЕКТЕ РИСКА РАЗВИТИЯ СПАЕЧНОЙ КИШЕЧНОЙ НЕПРОХОДИМОСТИ

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Резюме. Предупреждению послеоперационных спаек посвящены многочисленные экспериментальные, клинические и лабораторные исследования. С учетом этиологических факторов и механизмов формирования послеоперационных спаек для их предупреждения предложены самые разнообразные методы. Нами проанализированы отдаленные результаты оперативных вмешательств на органах брюшной полости у 317 пациентов, которые были прослежены в сроки до 18 месяцев. Основную группу составил 101 пациент, у которых для профилактики спайкообразования интраоперационно применялся препарат Хемобен. В группу сравнения включено 216 больных, которым выполнены вмешательства без применения каких-либо антиадгезивных средств. В отдаленный период (от 3 до 18 месяцев) после операции у 116 пациентов группы сравнения и 64 больных основной группы была проведена оценка уровня качества жизни с помощью специально разработанного для такой когорты пациентов опросника GIQLI (Gastrointestinal Quality of Life Index). Изучение субъективного фактора оценки противоспаечной эффективности по сравнительному анализу уровня качества жизни по опроснику GIQLI показало более высокое значение этого показателя в основной группе по всем основным доменам, при этом общий балл составил 103,8±9,8 против 92,6±10,8 баллов (t=7,12; p <0,05) (показатель в группе здоровых лиц составил 123,6±5,1 баллов).

Ключевые слова: *спаечная кишечная непроходимость; противоспаечные средства; качество жизни; препарат Хемобен.*

INTRODUCTION

The adhesions lead to decreased quality of life, chronic abdominal pain, and infertility. In some cases, an intestinal obstruction may develop [1–3].

In fact, adhesions are a specific pathologic response of the peritoneum to inflammation in patients with cholecystitis, peptic ulcer, salpingitis, oophoritis, endometriosis, and uterine myoma. Previously occurring adhesions are often the cause of infertility in patients with tubal and peritoneal forms of infertility.

Numerous experimental, clinical, and laboratory studies have been devoted to the prevention of postoperative adhesions. Taking into account etiologic factors and mechanisms of postoperative adhesions formation, a wide variety of methods have been proposed for their prevention [4–7].

The available "barriers" are not the panacea; the search for new methods continues. Also, some authors propose to continue the development of liquid substances for single intraperitoneal application, which will significantly reduce the incidence of postoperative adhesions. It will have a reasonable cost and there will not be any adverse effects on the coagulation system and wound healing processes [8–10].

MATERIALS AND METHODS

We analyzed the long-term results of surgical treatment of abdominal organs in 317 patients who were followed up to 18 months. The main group consisted of 101 patients in whom Hemoben was intraoperatively used to prevent adhesions. The control group included 216 patients, who underwent treatment without any anti-adhesive agents (Table 1).

As the result of the follow-up in the long-term period (18 months) it was possible to establish the development of clinical picture of acute adhesive intestinal obstruction (AAIO) in 2 (2.0%) patients of the main group, and in the control group — in 19 (8.8%) patients (Table 2). It should be noted, that in patients who had operated on for leaver and spleen injure with the use of Hemoben, in the long-term period the occurrence of clinical picture of AAIO was not noted in any case.

Only 1 (1.0%) patient of the main group and 8 (3.8%) patients of the comparison group underwent surgical intervention because of the AAIO (Table 3).

The data shows only clinically significant cases of postoperative adhesive intestinal obstruction.

Therefore, for a more objective analysis the study was supplemented with subjective assessment, which can also indirectly find the presence of adhesions affecting the patient's condition and their quality of life (QOL). For this purpose, in the period from 3 to 18 months after the surgical treatment, 116 patients of the comparison group and 64 patients of the main group were evaluated for their QOL using the Gastrointestinal Quality of Life Index (GIQLI) questionnaire, which

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Table 1. The number of followed-up patients depending on the time of follow-up

Таблица 1. Количество прослеженных больных в зависимости от сроков наблюдения

Период наблюдения / Observation period	Группа сравнения / Comparison group		Основная группа / The main group	
	абс. / abs.	%	абс. / abs.	%
Оперированы по поводу ОСКН / They were operated on for AAIO				
1 месяц / 1 month	12	11,5	7	25,0
6 месяцев / 6 months	31	29,8	14	50,0
12 месяцев / 12 months	46	44,2	4	14,3
18 месяцев / 18 months	15	14,4	3	10,7
Всего / Total	104	100,0	28	100,0
Оперированы на желудке и/или кишечнике / Operated on the stomach and/or intestines				
1 месяц / 1 month	14	19,4	11	20,4
6 месяцев / 6 months	24	33,3	21	38,9
12 месяцев / 12 months	23	31,9	14	25,9
18 месяцев / 18 months	11	15,3	8	14,8
Всего / Total	72	100,0	54	100,0
Оперированы по поводу травм печени или селезенки / They were operated on for injuries to the liver or spleen				
1 месяц / 1 month	7	17,5	4	21,1
6 месяцев / 6 months	11	27,5	9	47,4
12 месяцев / 12 months	15	37,5	4	21,1
18 месяцев / 18 months	7	17,5	2	10,5
Всего / Total	40	100,0	19	100,0
Все больные / All patients				
1 месяц / 1 month	33	15,3	22	21,8
6 месяцев / 6 months	66	30,6	44	43,6
12 месяцев / 12 months	84	38,9	22	21,8
18 месяцев / 18 months	33	15,3	13	12,9
Всего / Total	216	100,0	101	100,0

Примечание: ОСКН — острая спаечная кишечная непроходимость.
Note: AAIO — acute adhesive intestinal obstruction.

Table 2. The frequency of verification of the development of acute adhesive intestinal obstruction in the period from 1 to 18 months after surgery

Таблица 2. Частота верификации развития острой спаечной кишечной непроходимости в сроки от 1 до 18 месяцев после операции

Период наблюдения / Observation period	Группа сравнения / Comparison group		Основная группа / The main group	
	абс. / abs.	%	абс. / abs.	%
Оперированы по поводу ОСКН / They were operated on for AAIO				
1 месяц / 1 month	1	1,0	0	0,0
6 месяцев / 6 months	3	2,9	0	0,0
12 месяцев / 12 months	5	4,8	1	3,6
18 месяцев / 18 months	4	3,8	0	0,0
Всего / Total	13	12,5	1	3,6
Оперированы на желудке и/или кишечнике / Operated on the stomach and/or intestines				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	0	0,0	0	0,0
12 месяцев / 12 months	2	2,8	1	1,9
18 месяцев / 18 months	1	1,4	0	0,0
Всего / Total	3	4,2	1	1,9

Ending of the table 2/ Окончание табл. 2

Период наблюдения / Observation period	Группа сравнения / Comparison group		Основная группа / The main group	
	абс. / abs.	%	абс. / abs.	%
Оперированы по поводу травм печени или селезенки / They were operated on for injuries to the liver or spleen				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	0	0,0	0	0,0
12 месяцев / 12 months	2	5,0	0	0,0
18 месяцев / 18 months	1	2,5	0	0,0
Всего / Total	3	7,5	0	0,0
Все больные / All patients				
1 месяц / 1 month	1	0,5	0	0,0
6 месяцев / 6 months	3	1,4	0	0,0
12 месяцев / 12 months	9	4,2	2	2,0
18 месяцев / 18 months	6	2,8	0	0,0
Всего / Total	19	8,8	2	2,0
	χ^2=5,169; df=1; p=0,023			

Примечание: ОСКН — острая спаечная кишечная непроходимость.
Note: AAIO — acute adhesive intestinal obstruction.

Table 3. The number of patients with acute adhesive intestinal obstruction requiring surgery of the intestinal wall

Таблица 3. Число больных с острой спаечной кишечной непроходимостью, потребовавшей оперативного лечения

Период наблюдения / Observation period	Группа сравнения / Comparison group		Основная группа / The main group	
	абс. / abs.	%	абс. / abs.	%
Оперированы по поводу ОСКН / They were operated on for AAIO				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	1	1,0	0	0,0
12 месяцев / 12 months	2	1,9	1	3,6
18 месяцев / 18 months	2	1,9	0	0,0
Всего / Total	5	4,8	1	3,6
Оперированы на желудке и/или кишечнике / Operated on the stomach and/or intestines				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	0	0,0	0	0,0
12 месяцев / 12 months	1	1,4	0	0,0
18 месяцев / 18 months	1	1,4	0	0,0
Всего / Total	2	2,8	0	0,0
Оперированы по поводу травм печени или селезенки / They were operated on for injuries to the liver or spleen				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	0	0,0	0	0,0
12 месяцев / 12 months	1	2,5	0	0,0
18 месяцев / 18 months	0	0,0	0	0,0
Всего / Total	1	2,5	0	0,0
Все больные / All patients				
1 месяц / 1 month	0	0,0	0	0,0
6 месяцев / 6 months	1	0,5	0	0,0
12 месяцев / 12 months	4	1,9	1	1,0
18 месяцев / 18 months	3	1,4	0	0,0
Всего / Total	8	3,7	1	1,0

Примечание: ОСКН — острая спаечная кишечная непроходимость.
Note: AAIO — acute adhesive intestinal obstruction.

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Table 4. The level of quality of life (GIQLI) in a group of healthy individuals

Таблица 4. Уровень качества жизни (GIQLI) в группе здоровых лиц

Компонент оценки качества жизни / The quality of life assessment	Здоровые лица (n=12) / Healthy faces (n=12)			
	M	δ	Min	Max
Значимость симптомов / The significance of the symptoms	66,5	4,1	59	72
Физическая активность / Physical activity	23,3	1,7	21	26
Эмоциональная активность / Emotional activity	16,4	1,6	14	19
Социальная активность / Social activity	13,7	0,8	12	15
Реакция на оперативное лечение / Reaction to surgical treatment	3,8	0,5	3	4
Общий балл / Total score	123,6	5,1	116	132

Table 5. Assessment of the level of quality of life (GIQLI) after operations for acute adhesive intestinal obstruction

Таблица 5. Оценка уровня качества жизни (GIQLI) после операций по поводу острой спаечной кишечной непроходимости

Компонент оценки качества жизни / The quality of life assessment	Группа сравнения (n=52) / Comparison group (n=52)				Основная группа (n=21) / The main group (n=21)				t	
	M	δ	Min	Max	M	δ	Min	Max	значение / meaning	p
Значимость симптомов / The significance of the symptoms	47,3	9,5	29	67	54,8	8,1	41	70	3,37	**<0,05**
Физическая активность / Physical activity	16,1	2,6	11	21	17,8	2,2	13	22	2,78	**<0,05**
Эмоциональная активность / Emotional activity	12,1	2,7	7	17	12,7	2,2	9	16	0,96	>0,05
Социальная активность / Social activity	10,0	1,8	6	13	10,8	1,4	8	13	1,83	>0,05
Реакция на оперативное лечение / Reaction to surgical treatment	2,1	0,6	1	3	2,4	0,6	1	3	2,43	**<0,05**
Общий балл / Total score	87,6	10,2	64	111	98,4	8,8	82	115	4,50	**<0,05**

was specially developed for this cohort of patients.

Among the 5 components of the GIQLI questionnaire assessment, special importance was in parameters such as "Significance of symptoms" and "Reaction to surgical treatment", although other components were important ("Physical activity", "Emotional activity", and "Social activity"). Overall, all components provided a summative score for the QOL. For a more qualitative comparative analysis, a group of healthy persons (12 people) was also studied, whose indicators were considered as a reference for our two groups (Table 4). For convenience and more complete information, the given numerical data will reflect the mean (M), its standard deviation (δ), the sample minimum (Min) and the sample maximum (Max) in each group.

As control data, we took the results of the survey in 12 healthy individuals, whose quality of life indicators are presented in Table 4.

РЕЗУЛЬТАТЫ

CA comparative analysis of both group's quality of life after undergoing surgical treatment for AAIO showed reliable differences in four parameters: significance of symptoms, physical activity, and response to surgical treatment. These parameters were higher in the main group ($p < 0.05$) (Table 5).

However, in patients who underwent gastric or intestinal surgical treatment, physical activity was the same as in the control group. But other parameters did not differ in the reliability level from those in patients operated on for AAIO (Table 6).

Similar results are in patients who underwent surgical treatment of liver and spleen injuries, where also the quality of physical activity in both groups does not differ (Table 7).

However, the analysis of the cumulative assessment of the QOL after all the surgeries shows that indexes are higher in the patients of the main group ($p < 0.05$), and only for one index

("Emotional activity") there was no significant difference between two groups (Table 8).

Comparing, in the patients of the main group, where the anti-adhesive preparation Hemoben was applied, after various surgeries on the abdominal organs, indices of QOL are close to those in healthy people, and significantly higher ($t = 7,12$; $p < 0,05$) than in the patients of the comparison group (Fig. 1, 2).

CONCLUSIONS

Thus, clinical evaluation of prevention of postoperative AAIO in the abdominal cavity has shown that application of Hemoben biocoating both over parenchymatous organs at traumatic injuries and locally to the injury area of parietal and visceral peritoneum, in terms of 18 months following-up allowed to reduce the frequency of clinically significant cases of postoperative AAIO from 8.8% (in 19 out of 216 patients in the comparison group) to 2.0% (2 out of 101 patients in the main group). The largest proportion of patients (13 out of 19 and 1 out of 2, respectively) were after earlier surgical treatment of this complication. In turn, resolution of AAIO was observed in 11 out of 19 patients in the comparison group and in 1 out of 2 in the main group, whereas in 3.7% (8 patients) and 1.0%

Table 6. Quality of Life Assessment (GIQLI) after gastric and/or intestinal surgery

Таблица 6. Оценка уровня качества жизни (GIQLI) после операций на желудке и/или кишечнике

Компонент оценки качества жизни / The quality of life assessment	Группа сравнения (n=36) / Comparison Group (n=36)				Основная группа (n=29) / The main group (n=29)				t	
	M	δ	Min	Max	M	δ	Min	Max	значение / meaning	p
Значимость симптомов / The significance of the symptoms	51,7	9,6	34	70	59,4	8,8	46	75	3,40	**<0,05**
Физическая активность / Physical activity	18,6	2,6	14	23	19,6	2,0	15	24	1,72	>0,05
Эмоциональная активность / Emotional activity	13,6	2,8	9	18	13,9	2,1	11	18	0,52	>0,05
Социальная активность / Social activity	11,3	1,8	8	14	12,0	1,2	9	14	1,88	>0,05
Реакция на оперативное лечение / Reaction to surgical treatment	2,2	0,6	1	3	2,6	0,6	1	4	2,31	**<0,05**
Общий балл / Total score	97,3	10,3	78	121	107,7	8,5	93	124	4,10	**<0,05**

Table 7. Quality of Life Assessment (GIQLI) after surgery for liver and/or spleen injuries

Таблица 7. Оценка уровня качества жизни (GIQLI) после операций по поводу травм печени и/или селезенки

Компонент оценки качества жизни / The quality of life assessment	Группа сравнения (n=28) / Comparison group (n=28)				Основная группа (n=14) / The main group (n=14)				t	
	M	δ	Min	Max	M	δ	Min	Max	значение / meaning	p
Значимость симптомов / The significance of the symptoms	49,1	8,1	35	66	55,4	8,2	39	72	2,32	**<0,05**
Физическая активность / Physical activity	20,3	2,6	16	25	21,3	2,6	17	26	1,15	>0,05
Эмоциональная активность / Emotional activity	13,3	2,2	9	17	13,6	1,8	11	17	0,44	>0,05
Социальная активность / Social activity	11,0	1,3	9	13	11,8	1,3	9	13	1,85	>0,05
Реакция на оперативное лечение / Reaction to surgical treatment	2,1	0,6	1	3	2,5	0,5	2	3	2,39	**<0,05**
Общий балл / Total score	95,8	8,5	80	111	104,5	9,2	88	119	2,96	**<0,05**

Table 8. Summary assessment of the quality of life (GIQLI) after all operations

Таблица 8. Сводная оценка уровня качества жизни (GIQLI) после всех операций

Компонент оценки качества жизни / The quality of life assessment	Группа сравнения (n=116) / Comparison group (n=116)				Основная группа (n=64) / The main group (n=64)				t	
	M	δ	Min	Max	M	δ	Min	Max	значение / meaning	p
Значимость симптомов / The significance of the symptoms	49,1	9,3	29	70	57,0	8,6	39	75	5,71	**<0,05**
Физическая активность / Physical activity	17,9	3,1	11	25	19,3	2,5	13	26	3,43	**<0,05**
Эмоциональная активность / Emotional activity	12,8	2,7	7	18	13,4	2,1	9	18	1,61	>0,05
Социальная активность / Social activity	10,7	1,8	6	14	11,5	1,4	8	14	3,71	**<0,05**
Реакция на оперативное лечение / Reaction to surgical treatment	2,1	0,6	1	3	2,5	0,6	1	4	4,36	**<0,05**
Общий балл / Total score	92,6	10,8	64	121	103,8	9,8	82	124	7,12	**<0,05**

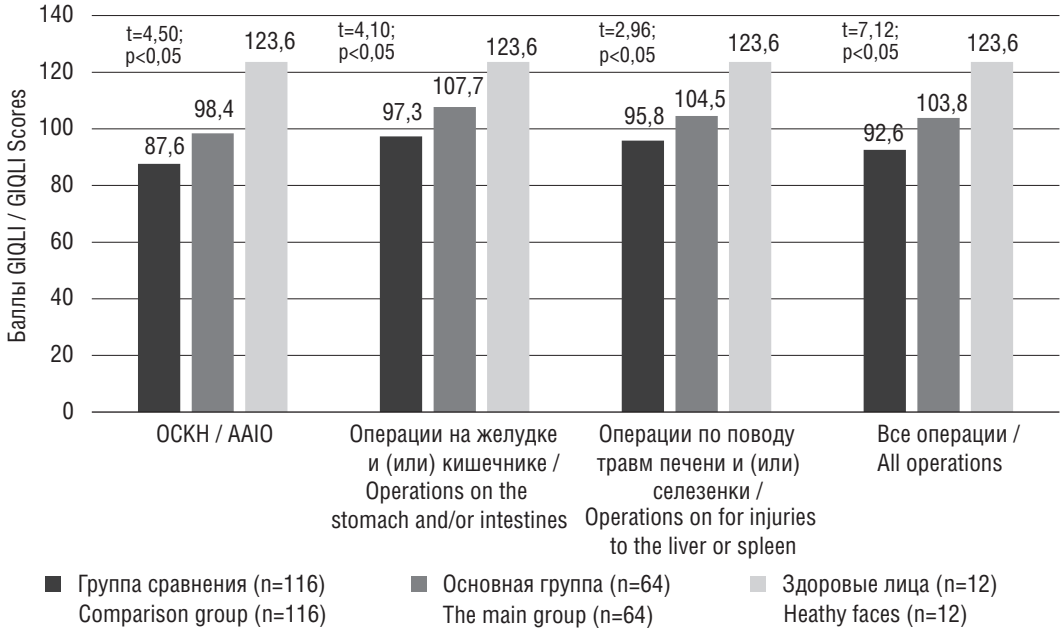

Fig. 1. Comparative indicators of the quality of life index (total GIQLI scores) depending on the operation. AAIO – acute adhesive intestinal obstruction. "P" values are reported between study groups

Рис. 1. Сравнительные показатели индекса качества жизни (общие баллы по GIQLI) в зависимости от перенесенной операции. ОСКН – острая спаечная кишечная непроходимость. Значение «p» приведено между группами исследования

(1 patient) of cases, respectively, this complication required surgical treatment. The comparative analysis of the level of QOL according to the GIQLI questionnaire showed a higher value of this indicator in the main group, which was indicated in the study of the subjective factor of anti-adhesive effectiveness. Thus, 4 out of 5 domains showed a higher value of QOL, in particular, according to the criterion "Significance of symptoms" the index in the comparison group amounted to 49,1 ± 9,3 points, and in the main group — 57,0 ± 8,6 points (t = 5,71; p < 0,05); "Reaction to surgical treatment" — 2,1 ± 0,6 vs. 2,5 ± 0,6 points (t = 4,36; p < 0.05); "Physical activity" — 17.9 ± 3.1 vs 19.3 ± 2.5 points (t = 3.43; p < 0.05) and "Social activity" — 10.7 ± 1.8 vs 11.5 ± 1.4 points (t = 3.71; p < 0.05), and only for the "Emotional activity" domain the difference was not significant — 12.8 ± 2.7 vs 13.4 ± 2.1 points (t = 1.61; p > 0.05). Overall, the total score was higher in the main group — 103.8 ± 9.8 vs 92.6 ± 10.8 points (t = 7.12; p < 0.05), which gene-

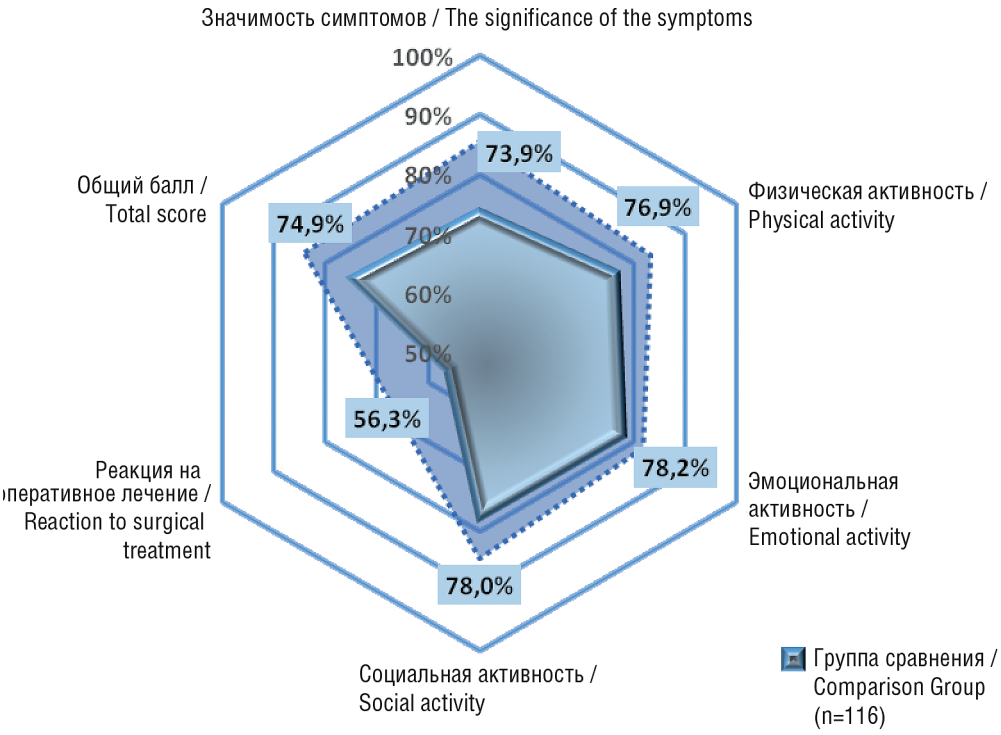

Fig. 2. The ratio of the quality of life indicator in the study groups in relation to healthy individuals

Рис. 2. Соотношение показателя качества жизни в группах исследования по отношению к здоровым лицам

rally provided a higher compliance with the group of healthy individuals (123.6 ± 5.1 points), amounting to 74.9% in the comparison group and 84.0% in the main group.

SUMMARY

The clinical evaluation of the prevention of the development of postoperative AAIO in the abdominal cavity showed that the application of Hemoben bio-coating both over the parenchymatous organs at traumatic injuries and locally to the injury area of the parietal and visceral peritoneum, in 18 months follow-up allowed to reduce the frequency of development of clinically significant cases of postoperative AAIO from 8.8 to 2.0%, while in 3.7 and 1.0% of cases, respectively, the mentioned complication required surgical treatment.

The study of subjective factor of anti-adhesive efficacy assessment by the comparative analysis of the level of QOL according to the GIQLI questionnaire showed a higher value of this index in the main group in all main domains, except for the level of the component "Social activity", and the total score amounted to 103.8 ± 9.8 vs 92.6 ± 10.8 points ($t = 7.12$; $p < 0.05$), which in general provided a higher correspondence to the group of healthy individuals (123.6 ± 5.1 points), amounting 74.9% in the comparison group and 84.0% in the main group.

ADDITIONAL INFORMATION

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

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

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

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов

интересов, связанных с публикацией настоящей статьи.

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FEATURES OF BODY COMPOSITION IN CHILDREN WITH DIFFERENT DEGREES OF OBESITY

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Abstract. *Introduction.* Bioimpedansometry is one of the methods that describes the absolute and relative amount of muscle and fat tissue, water sectors of the body. Determining the patterns of changes in the component composition of the body depending on the degree of obesity in children will improve the efficiency of therapeutic actions aimed at reducing body weight. *The aim:* to estimate the features of component composition of the body in children with varying degrees of obesity. *Materials and methods.* 152 children 7–17 years of age with obesity took part in one-time research based on the Clinic of Saint Petersburg State Pediatric Medical University: 27 people with I degree, 50 people with II degree, 42 with III degree and 33 had morbid obesity. The control group consisted of 25 healthy children without obesity. For evaluating the composition of the body, the "ABC-01 MEDASS-device" was used, St. Petersburg. The main indicators were estimated: body fat mass and it's share, lean body mass, active cell mass and it's share, skeletal muscle mass and it's share, specific basal metabolic rate, total body water and extracellular water. *Results.* The proportion of body fat mass at I–II degrees is not expressed and increases by 12–16% at III–IV degrees of obesity. The lean body mass increases with increasing the degree of obesity: I degree — 22.3% increasing; II degree — 42.1% increasing, III degree — 51.1% increasing, IV degree (morbid obesity) — 73% increasing. The indicator of Active cell mass decreases as the degree of obesity increases. The deviation of active cell mass in children with I degree of obesity was lower by 9.4% compared to the control group, with II degree — by 11.8%, with III degree — by 16.6%, with IV degree (morbid) — by 21.15%. The incidence of "sarcopenic obesity" (decrease in skeletal muscle mass and its proportion): in 25.5% of children with morbid obesity, in 20.5% with III degree and 10% with II degree. The indicator of total body water in children with I–II degrees of obesity is the same and increased by 24.7%, with III degrees — by 44.1%, with IV degrees (morbid) — by 63%. *Conclusion.* Obesity has an influence on the body composition parameters in children. These changes are different and depend on the degree of obesity. The most expressed disorders are observed in adolescents with long-term morbid obesity.

Key words: *children; obesity; degree of obesity; body composition.*

ОСОБЕННОСТИ КОМПОЗИЦИОННОГО СОСТАВА ТЕЛА У ДЕТЕЙ С РАЗЛИЧНОЙ СТЕПЕНЬЮ ОЖИРЕНИЯ

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Резюме. *Введение.* Биоимпедансометрия является одним из методов, описывающих абсолютное и относительное количество мышечной и жировой ткани, водных секторов организма. Определение закономерностей изменения компонентного состава тела в зависимости от степени ожирения у детей позволит повысить эффективность терапевтических мероприятий, направленных на снижение массы тела. *Цель:*

оценить особенности композитного состава тела у детей с различной степенью ожирения. *Материалы и методы.* Проведено одномоментное исследование, в котором приняло участие 152 ребенка в возрасте 7–17 лет с ожирением на базе клиники ФГБОУ ВО СПбГПМУ Минздрава России: 27 человек с I степенью, 50 человек со II степенью, 42 — с III степенью и 33 имели морбидное ожирение. Группу контроля составили 25 здоровых детей без ожирения. Для оценки композиционного состава тела был использован аппарат «АВС-01 МЕДАСС», г. Санкт-Петербург. Оценивали основные показатели: жировая масса тела (ЖМТ) и ее доля, безжировая (тощая) масса (БМТ) тела, активная клеточная масса (АКМ) и ее доля, скелетно-мышечная масса (СММ) и ее доля, удельный основной обмен (УОО), общая вода в организме (ОВО), внеклеточная жидкость (ВКЖ). *Результаты.* Доля ЖМТ при I–II степени не различается и увеличена на 12–16% при III–IV степени. Количество БМТ повышается с увеличением степени ожирения: I степень — превышение на 22,3%; II степень — на 42,1%, III степень — на 51,1%, IV степень (морбидное) — на 73%. Показатель АКМ по мере возрастания степени ожирения снижается: у детей с I степенью ожирения отклонение АКМ по сравнению с группой контроля было ниже на 9,4%, со II степенью — на 11,8%, с III степенью — на 16,6%, с IV степенью (морбидное) — на 21,15%. Частота встречаемости «саркопенического ожирения» (снижение СММ и ее доли): у 25,5% детей с морбидным ожирением, у 20,5% — с III степенью и 10% — со II степенью. Уровень УОО и ВКЖ не зависят от степени ожирения. Показатель ОВО у детей с I–II степенью одинаковый и увеличен на 24,7%, с III степенью — на 44,1%, с IV степенью (морбидное) — на 63%. *Заключение.* Ожирение влияет на изменение параметров композиционного состава тела у детей. Эти изменения различны и зависят от степени ожирения. Наиболее выраженные нарушения наблюдаются у подростков с длительно текущим морбидным ожирением.

Ключевые слова: *дети; ожирение; степень ожирения; композиционный состав тела.*

INTRODUCTION

According to the World Health Organization (WHO), obesity is the most common chronic disease in the world. The medical community is concerned about its progressive growth among children. This indicator in the Russian Federation has reached 27% in 2022 year [1, 2]. The importance of obesity in pediatrics is determined by the unfavorable prognosis in the form of the development of metabolic disorders and comorbid pathology [2–4]. The determination of body mass index (BMI) is recommended as a diagnostic criterion of obesity in children [5]. However, its estimation is not always sufficient because it does not reflect the ratio between the components of body weight (lean and fat mass). It is difficult to directly estimate the amount of fad tissue in the body; for this purpose, bioimpedance analysis of body composition (BIA) is used. It is a non-invasive and widely available medical diagnostic technology for analyzing the body composition (volumes of water score, lean and fat mass, active cell mass, etc.) and objective assessment of a person's nutritional status. It is based on measuring the electrical resistance of tissues (impedance) when a low-intensity electric current passes through them [6]. The use of BIA allows to create an optimal complex of effects on effective weight loss with control of markers in dynamics [7–10]. In recent years, the number of scientific publications related to body composition studies about obesity in children was increased [11–13]. Nevertheless, the issue of changes and differences in the content of bone, fat and muscle mass depending on the class of obesity has not been fully studied.

THE AIM OF THE STUDY

To evaluate the features of body composition in children with different classes of obesity.

MATERIALS AND METHODS

In the one-stage study, 152 children with obesity aged 7–17 years were examined (boys: n = 73; girls: n = 79) in clinic of FSBEI HE SPbSPMU of the Ministry of Healthcare of the Russian Federation. The class of obesity was taken as the basis for dividing patients into groups:

- Group 1 — children with I class of obesity (17.7%; n = 27);
- Group 2 — children with the II class of obesity (33%; n = 50);
- Group 3 — children with III class of obesity (27.6%; n = 42);
- Group 4 — children with IV class (morbid) of obesity (21.7%; n = 33).

The control group consisted of 25 children without obesity.

All patients underwent standard clinical and laboratory examination. To assess body composition, we used an AVS-01 MEDASS device (St. Petersburg) connected to a personal computer with installed software. The study was performed

while patients were lying on the back with the correct position of electrodes.

The main indices were evaluated in absolute numbers and percent of deviation from the norm: Body fat mass (BFM, kg), percentage of deviation from normal BFM, fraction of fat mass (BFM,%), percentage of deviation from normal BFM fraction, fat-free (lean) body mass (FFM, kg), percentage of deviation from normal BFM, active cell mass (ACM, kg), fraction of active cell mass (ACM,%), percentage of deviation from normal ACM fraction, skeletal muscle mass (SMM, kg), percentage of deviation from the normal SMM, fraction of skeletal muscle mass (SMM,%), percentage of deviation from the normal SMM fraction, specific basic metabolism rate (SBM, kcal/m per day), percentage of deviation from the normal SBM, basic metabolism rare (BM, kcal/day), total body water (TBW, kg), percentage of deviation from the norm of TBW, extracellular fluid (ECF, kg), percentage of deviation from the norm of ECF. A statistical processing was performed using the program STATISTICA 10.0 (StatSoft Inc., USA). All data are presented as median and interquartile range, because the most of studied parameters did not have an approximate-normal distribution. The Mann-Whitney test was used to assess the reliability of differences between the studied groups. A correlation analysis was performed using Spearman's criterion. The critical level of significance of differences was accepted as $p \leq 0.05$.

RESULTS AND DISCUSSION

The height values in the studied groups of children with obesity were 159.7 [120;198] cm. The physical development above average and high was found in 76% of adolescents. The body weight values in the main group were 84.3 [40.8;169] kg. The waist circumference was 100 [85;115] cm and hip circumference was 98 [91;105] cm. The distribution of subcutaneous fat tissue was uneven, with an emphasis on the abdomen. The sexual development of the children corresponded to II–V stages according to Tanner.

Fat mass

There was excess of fat mass in children with obesity compared to the control group ($p = 0.03$) (Fig. 1).

The excess of fat mass compared to the control group in children with I-II classes was in 8.4%, with III class — 12.7%, with IV class — 16.2% ($p = 0.01$).

There was a direct perfect correlation between BFM and BMI ($r = 0.95$), FFM ($r = 0.91$). A moderate correlation was found between BMI and FFM

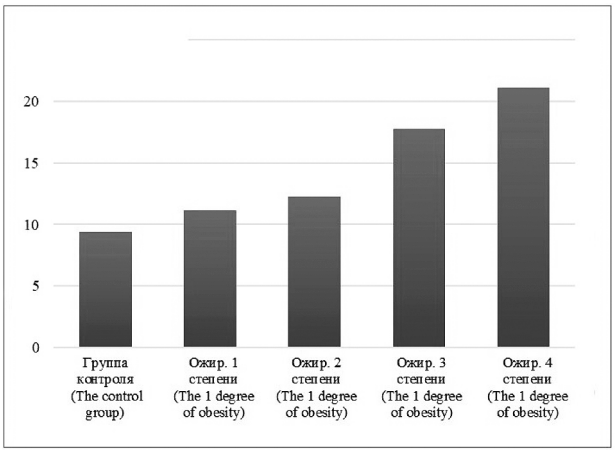

Fig. 1. Mean values of fat mass (kg) in obese children and in the control group

Рис. 1. Средние значения жировой массы (кг) у детей с ожирением и в группе контроля

Table 1. Amount of lean mass in children with different degrees of obesity

Таблица 1. Количество тощей массы у детей с различной степенью ожирения

Исследуемая группа / The study group	Среднее значение количества тощей массы, кг / The mean of lean mass, kg	Превышения БМТ по сравнению с группой контроля, % / The excesses of the lean body mass compared to the control group, %
Группа контроля / The control group	40,25	
Ожирение I степени / The I degree of obesity	49,22	22,3%
Ожирение II степени / The II degree of obesity	57,19	42,1%
Ожирение III степени / The III degree of obesity	60,82	51,1%
Ожирение IV степени / The IV degree of obesity	69,63	73%

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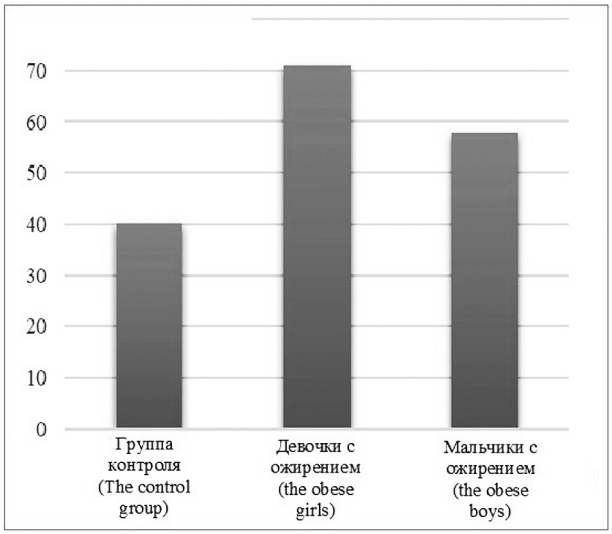

Fig. 2. Mean values of lean mass percentage (kg) in obese girls and boys and in the control group

Рис. 2. Средние значения доли тощей массы (кг) у девочек и мальчиков с ожирением и в группе контроля

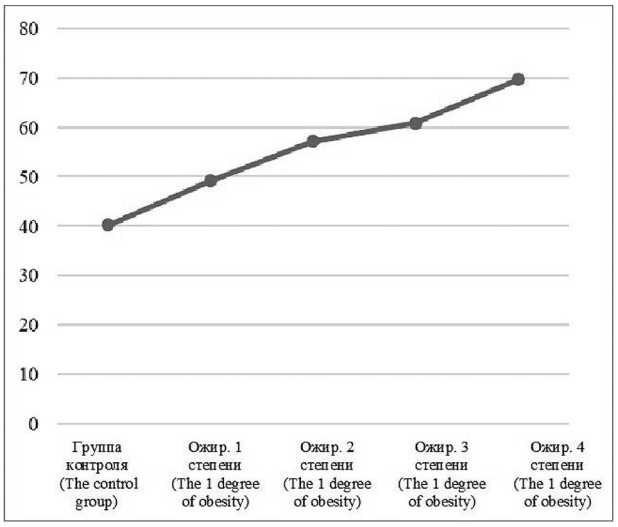

Fig. 3. Level of deviation of lean mass percentage (%) in children with different degrees of obesity

Рис. 3. Уровень отклонения доли тощей массы (%) у детей с различной степенью ожирения

(r = 0.61), which indicates that the increase in BMI in overweight and children with obesity is mainly due to an increase in BFM. To a lesser extent BMI in children with obesity is affected by FFM.

Lean body mass (fat-free mass)

The mean values of FFM in children in the studied groups are presented in Table 1.

A statistically significant excess of FFM was found in 30% of adolescents (13–17 years old) with obesity (p = 0.0001). There was a significant difference in the value of FFM excess. It was 72,9% in girls and 41,3% in boys (p = 0.02) (Figure 2).

The percentage of FFM deviation was not the same in groups of different classes of obesity, in all groups it was exceeded: in group 1 — 22.3%; in group 2 — 42.1%; in group 3 — 51.1% and in group 4 — 73% (p = 0.003) (Figure 3).

Active cell mass

Active cell mass (ACM) includes actively metabolizing muscle cells, cells of internal organs, and nervous tissue. The ideal proportion of ACM is 50–56% [6]. The importance of maintaining normal ACM is confirmed by a number of studies, according to them, the ACM is a needed part to lose a fat mass in the process of reducing body weight.

A decrease in the number of metabolically active cells leads to a decrease in the metabolic rate and causes a constant feeling of hunger, signaling that the cells of the body are undernourished despite the large amount of energy scores in the body [2].

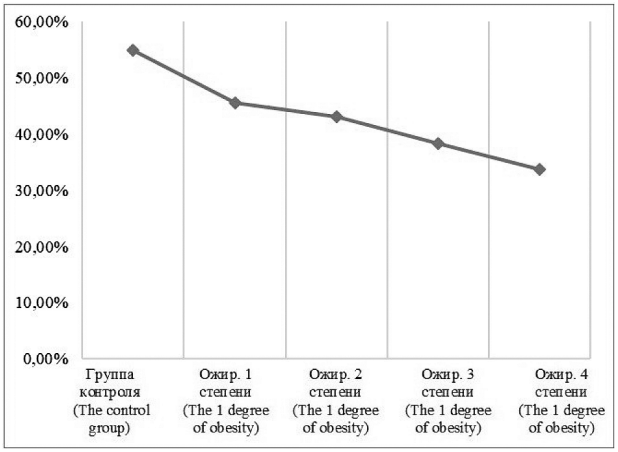

Fig. 4. Dependence of ACM level on the degree of obesity

Fig. 4. Dependence of ACM level on the degree of obesity

If we think that children with obesity experience a greater sense of hunger compared to children with normal body weight, it can be argued that low levels of ACM are a serious problem in the weight loss process.

There is a tendency: the ACM decreases if the degree of obesity increases. In children with class I of obesity, the deviation of ACM compared to the control group was lower by 9.4%, with class II — by 11.8%, with class III — by 16.6%, with class IV — by 21.15% (p = 0.003) (Fig. 4).

Skeletal muscle mass

In 56% of the examined children with obesity, a decrease in the level of SMM and its fraction was detected (p ≤ 0.05). A normal fraction of SMM was

found in 29% and in 15% was increased ($p \leq 0,05$). The condition of progressive loss of muscle mass is most studied in elderly patients and children with oncologic diseases, cerebral palsy, in the postoperative period and is called "sarcopenia" [9, 10]. The "Sarcopenia" on the background of obesity in children is a poorly studied problem and deserves a special attention [10]. The frequency of "sarcopenia" increased with increasing of class of obesity: a 25.5% of the examined patients with decreased SMM had IV class of obesity (morbid), 20.5% — III class and 10% — III class (Fig. 5). The 88.1% of the examined children with low SMM had a long (> 5 years) course of obesity diagnosed at an early age, progressing in puberty.

Specific basic metabolism

When evaluating the SBM, it was found that in the group of patients with obesity the values were higher than in the control group. A study of correlations demonstrates a direct relationship between the level of ACM in the main group of children with obesity and the level of SBM in this group ($r = 0.84$). A weak direct correlation ($r = 0.27$) was found between the level of SBM and BFM, indicating an increase in SBM in children with obesity due to an increase in the number of metabolizing cells rather than adipose tissue. No statistically significant differences in the level of SBM depending on the degree of obesity were found.

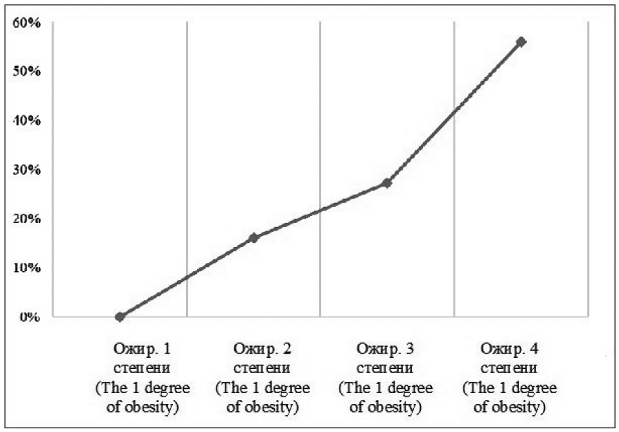

Fig. 5. Frequency of "sarcopenia" among children with different degrees of obesity

Рис. 5. Частота «саркопении» среди детей с различной степенью ожирения

Total body water

In 100% of cases, an excess of TBW was found in children with obesity compared to children of the control group (Table 2).

If the class of obesity increases, there are an increase in TBW, in girls largely than in boys (70.2 and 41%, respectively) ($r = 0.91$, $p = 0.001$). In children with I–II classes it was by 24.7%, with III class — by 44.1%, with IV class — by 63% ($r = 0.92$, $p = 0.002$). There was a difference in the degree of TWO excess between boys and girls with IV class of obesity by 39.7 and 67.3%, respectively ($p = 0.0002$).

According to a number of researchers, the specific weight of water in adipose tissue is much lower than in muscle tissue [6]. Thus, the muscle mass makes the greatest contribution to the increase in the level of TWO, which is confirmed by the correlation between the ACM and value of total water ($r = 0.9$).

Extracellular fluid

The change of ECF value was found in children with obesity of high school age only (15-17 years old). The decrease in the amount of ECF was found in 26% of children with III-IV classes of obesity and increase — in 6.2% ($p = 0.001$).

CONCLUSION

Obesity makes a significant contribution to changes in body composition in children. The

Table 2. Mean values of total body water in obese children compared to the control group

Таблица 2. Средние значения ОВО у детей с ожирением по сравнению с группой контроля

Исследуемая группа / The study group	Среднее значение уровня ОВО, кг / Mean values of total body water, kg	Превышения по сравнению с группой контроля, % / The excesses compared to the control group, %
Группа контроля / The control group	44,3	
Ожирение I степени / The I degree of obesity	54,75	23,61
Ожирение II степени / The II degree of obesity	55,24	24,7
Ожирение III степени / The III degree of obesity	63,84	44,11
Ожирение IV степени / The IV degree of obesity	72,21	63

changes are different and depend on the class of obesity. The most pronounced disorders are observed in adolescents with long-term morbid obesity.

1. The proportion of BFM is not different in I–II classes of obesity and increased by 12–16% in III–IV classes.

2. The amount of FFM increases with increasing of class of obesity: in the I class, it exceeded by 22.3%, II class — 42.1%, III class — 51.1% and III class (morbid) — 73%.

3. The ACM value decreases with increasing of the class of obesity: in children with I class of obesity, the deviation of ACM compared to the control group was lower by 9.4%, with II class — by 11.8%, with III class — by 16.6%, with IV class (morbid) — by 21.15%.

4. The frequency of "sarcopenic obesity" (decreased SMM and its proportion): in 25.5% of children with morbid obesity, in 20.5% with III class and in 10% with II class.

5. The levels of SBM and ECF are independent of the class of obesity.

6. The TBW in children with I-II classes of obesity is the same and increased by 24.7%, with III class — by 44.1%, with IV class (morbid) — by 63%.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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MONITORING OF RENAL TISSUE OXYGENATION IN YOUNG CHILDREN WITH CONGENITAL HEART DISEASE IN THE PERIOPERATIVE PERIOD

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Abstract. *Introduction.* Tissue oximetry is one of the most promising methods for assessing the efficiency of systemic perfusion in children in critical condition, which is especially true for newborns with heart defects, but it is not a routine method of diagnosing systemic hypoperfusion in neonatal intensive care units, which requires its wider implementation. The *aim of the study* is to demonstrate the possibilities of prolonged NIRS-monitoring of renal tissue oxygenation to determine further tactics of management of newborns with congenital heart disease. *Patients and methods.* Three clinical cases of prolonged noninvasive monitoring of renal oxygenation in infants with congenital heart disease accompanied by systemic hypoperfusion in the perioperative period are presented. *Results.* It was demonstrated that on the basis of renal tissue oxygenation indices it is possible to make an informed decision on the correction of intensive care measures and the need for emergency cardiac surgery. In some cases, NIRS-monitoring allows to avoid early intubation and invasive ventilation of lungs, which is reflected in the description of the third case. *Conclusion.* Noninvasive real-time bedside monitoring of tissue oxygenation is a highly effective method of diagnosing systemic hypoperfusion and should be more widely used in neonatal intensive care units, especially in neonates with CHD, in whom the risk of shock of various genesis is extremely high.

Key words: *tissue oximetry; neonate; critical congenital heart disease; systemic hypoperfusion.*

МОНИТОРИНГ ОКСИГЕНАЦИИ ТКАНЕЙ ПОЧЕК У ДЕТЕЙ РАННЕГО ВОЗРАСТА С ВРОЖДЕННЫМИ ПОРОКАМИ СЕРДЦА В ПЕРИОПЕРАЦИОННОМ ПЕРИОДЕ

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Резюме. *Введение.* Тканевая оксиметрия является одним из наиболее перспективных методов оценки эффективности перфузии у детей в критическом состоянии, что особенно справедливо для новорожденных с пороками развития сердца, однако она не является рутинным методом диагностики в неонатальных отделениях реанимации и интенсивной терапии, что требует ее более широкого внедрения. *Цель исследования* — демонстрация возможностей продленного NIRS-мониторинга оксигенации тканей почек с целью

определения дальнейшей тактики ведения новорожденных с врожденными пороками сердца. *Пациенты и методы.* Представлены три клинических случая применения продленного неинвазивного мониторинга почечной оксигенации у детей раннего возраста с врожденными пороками сердца, сопровождающимися системной гипоперфузией, в периоперационном периоде. *Результаты.* Продемонстрировано, что оценка показателей оксигенации тканей почек позволяет принять обоснованное решение о коррекции мероприятий интенсивной терапии и необходимости проведения экстренного кардиохирургического вмешательства. В ряде случаев NIRS-мониторинг позволяет избежать раннего перевода пациента на инвазивную вентиляцию легких, что отражено в описании третьего случая. *Заключение.* Неинвазивный прикроватный мониторинг тканевой оксигенации в режиме реального времени является высокоэффективным методом диагностики системной гипоперфузии и должен более широко использоваться в отделениях неонатальной реанимации и интенсивной терапии, особенно у новорожденных с врожденным пороком сердца, у которых риск развития шока различного генеза крайне высок.

Ключевые слова: *тканевая оксиметрия; новорожденные; критические врожденные пороки сердца; системная гипоперфузия.*

INTRODUCTION

The use of near-infrared spectroscopy to assess the adequacy of cerebral perfusion and oxygenation was first proposed by F.F. Jobsis in 1977 [1]. Subsequently, his idea was implemented by creating monitors to assess the saturation of brain tissue and other internal organs with oxygen.

The principle of the NIRS method is based on the ability of tissues to transmit light in the range close to the infrared spectrum (740–3000 nm), this ability is maximum in the range of 600–1000 nm. As a light beam passes through the tissues of internal organs, pigment compounds known as chromophores absorb light. Human tissues contain many components for which absorption spectra of light with a wavelength close to the infrared range have been well studied, the concentration of which varies depending on tissue oxygenation and the level of oxyhemoglobin, deoxyhemoglobin and cytochrome a-a3. In addition to oxyhemoglobin and deoxyhemoglobin, other hemoglobin compounds, in particular carboxyhemoglobin, are also capable of absorbing a light beam in a spectrum close to infrared radiation, but under physiological conditions the overall error in the absence of taking into account the optical properties of these compounds does not exceed 1% [2, 3]. The venous component accounts for approximately 75–85% of the blood flow volume, and since monitoring using NIRS technology is not dependent on the presence of a pulse wave, the data obtained during the study reflects the weighted average (75–85% venous) oxyhemoglobin concentration of the studied area [4]. Numerous factors can influence NIRS values, but the two main ones are tissue perfusion and tissue oxygen utilization. Thus, NIRS indirectly reflects the balance between oxygen delivery and oxygen consumption. Since the tissue oximeter signal propagates according to the Beer–Lambert Law, which states that a parallel monochromatic beam of light attenuates as it propagates through an absorbing medium and reflects information about vessels with a diameter of less than 1 mm, the monitoring is a convenient tool for assessing visceral perfusion, which is beneficial distinguishes it from Doppler ultrasound, which allows one to evaluate the efficiency of blood flow in larger blood vessels at a limited point in time [5].

First of all, this monitoring method became widespread in neurosurgery; later, the cerebral NIRS monitoring began to be used in various branches of medicine [6]. In particular, in cardiac surgery it is used as the only option for neuromonitoring or as part of combined neuromonitoring during cardiac surgery. It has been established that the use of parainfrared spectroscopy during cardiac surgery with cardiopulmonary bypass makes it possible to detect episodes of cerebral ischemia with a higher frequency than previously thought, which, in turn, can significantly reduce the frequency of cerebral-vascular intraoperative complications in cardiac surgery [7–9].

Since 1980, studies have appeared on the effectiveness of using NIRS to monitor cerebral, tissue and organ perfusion in newborns and young children [10, 11]. A radiation close to the infrared spectrum is absorbed mainly in the dermis, but about 30% of the light flux penetrates to a depth of 30 mm, reaching the subcutaneous fat layer and the organs located underneath it [12]. This penetrating ability of para-infrared radiation, on the one hand, and the insignificant thickness of the integumentary tissues in newborns, on the

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other, make it possible to evaluate the effectiveness of oxygenation and perfusion of the kidneys, intestines, liver, muscles and brain [13, 14].

Currently, there are many studies on the use of cerebral oximetry in young children with congenital heart defects (CHDs) during cardiac surgery with cardiopulmonary bypass. Special protocols have been developed that take into account cerebral oximetry indicators to determine clinical tactics during cardiac surgery in order to improve long-term neurological prognosis [15–19].

There are studies of organ perfusion in premature newborns for the purpose of early diagnosis of necrotizing enterocolitis, one of which demonstrated that regional oximetry indices of the abdominal region correlate with volume-velocity characteristics in the superior mesenteric artery obtained by Doppler study [20]. Several studies have noted that preterm infants with clinical necrotizing enterocolitis (NEC) had lower abdominal oxygenation values and less variability from baseline compared to controls [21, 22]. The effectiveness of the use of parainfrared spectroscopy in children with congenital heart disease has been proven as a predictor of the development of NEC in the postoperative period [23]. A.G. DeWitt et al. demonstrated the possibility of prolonged monitoring of organ perfusion using parainfrared spectroscopy to assess the risks of developing necrotizing enterocolitis in newborns with congenital heart disease, including those with a functionally single ventricle [24]. The study included 64 newborns who underwent biventricular correction of congenital heart disease or palliative interventions. In the postoperative period, organ blood flow was monitored before and during the initiation of enteral feeding to determine whether changes in the obtained parameters are associated with the risk of developing necrotizing enterocolitis. The proven necrotizing enterocolitis or suspicion of it was noted in 32% of patients with a functionally single ventricle, while it was absent in children with biventricular correction, which was statistically significant ($p = 0{,}001$). Compared with patients with or without suspected NEC, children with proven NEC had lower rates of splanchnic rSO_2 (32.6% vs. 47%; $p = 0{,}05$).

The advantage of the method is non-invasiveness and safety for patients, no restrictions on the duration of use, the ability to assess tissue oxygenation in real time, which allows you to monitor changes during therapeutic measures that affect vascular resistance, the balance of pulmonary and systemic blood flow. At the same time, it should be noted that, according to some experts, there are difficulties in determining the critical values of organ perfusion indicators and eliminating artifacts that arise when the patient moves, which limits the use of NIRS for monitoring splanchnic blood flow [25].

Despite the potential of NIRS monitoring in cardiac anesthesiology, including in newborns with congenital heart disease, this technique has not been widely used in the practice of intensive care units to assess the effectiveness of organ perfusion [26, 27].

It should be noted that newborns with CHDs who are at high risk of severe impairment of systemic perfusion, which makes continuous monitoring of renal oxygenation the most promising method for assessing changes in regional blood flow even before irreversible organ damage occurs.

We believe that the currently available data, despite some limitations, make it possible to use the assessment of tissue oxygenation and perfusion as a useful tool for improving the effectiveness of intensive care measures in children with CHDs and hemodynamics of the functionally single ventricle [24].

AIM OF THE STUDY

To demonstrate the possibilities of extended NIRS monitoring of kidney tissue oxygenation in order to determine further tactics for the management of newborns with congenital heart disease.

PATIENTS AND METHODS

Three clinical cases of the use of prolonged non-invasive monitoring of renal oxygenation in young children with congenital heart defects accompanied by systemic hypoperfusion in the perioperative period are presented.

The sensor for assessing regional renal oxygenation was placed according to the recommendations of M.W. Harer et al. (2020): below the costal arch and above the iliac crest, with the tip of the sensor located lateral to the spine and the reading end of the sensor wrapped around the lateral surface (Fig. 1) [27].

Clinical case № 1

Newborn boy, 1 month of life. Diagnosis: congenital heart disease, critical aortic valve stenosis. Atrial septal defect. Patent ductus arteriosus. Ductus-dependent systemic circulation. The

mother's medical history is unremarkable. 2nd term birth at 41 weeks and 1 day. The diagnosis was confirmed by echocardiography (EchoCG) and multislice computed tomography (MSCT). On the 7th day of life, open aortic commissurotomy and planar resection of the leaflets were performed under artificial circulation. In the postoperative period, there was a dependence on high positive end-expiratory pressure (PEEP) in the range of 7–8 mm H2O. When trying to reduce parameters — clinical and radiological picture of pulmonary edema, inotropic support, intolerance to enteral nutrition due to the persistent clinical picture of intestinal paresis, the need for constant stimulation of diuresis with high doses of loop diuretics, and the development of chyloperitoneum were observed. An chocardiography revealed mitral valve insufficiency of grade II–III. Despite conservative therapy, these manifestations persisted. According to the assessment of organ blood flow using Doppler ultrasonography against the background of analgosedation, minimal reverse was noted in the renal arteries and vertebrobasilar arteries (VBA), which did not correspond to the existing clinical picture. In order to assess the significance of mitral regurgitation and the accompanying hypoperfusion of the abdominal organs and kidneys over the time, continuous extended NIRS monitoring of renal blood flow was initiated.

According to the monitoring results, significant hypoperfusion was revealed — average saturation values according to monitoring data were 53–55% lower than transcutaneous pulse oximetry values, average values were 43–47%, with regular episodes of desaturation up to 25–28% upon awakening and activation of the patient. Based on the totality of clinical and instrumental data, a decision was made to perform a repeat surgical intervention. At the age of 1.5 months of life, the mitral valve replacement was performed with a mechanical prosthesis "Carbomedix" with a diameter of 16 mm, revision of the aortic valve, planar resection of the aortic valve leaflets under conditions of cardiopulmonary bypass (CPB) and cardioplegia (CP). The early postoperative period was unremarkable. The ionotropic support was stopped on the 2nd day after surgery. On the 10th day of the perioperative period, the patient was extubated, transferred to non-invasive artificial ventilation, and against the background of regression of intestinal paresis, enteral nutrition was started with a gradual expansion to the full age requirement within three weeks. On the 20th day, the respiratory support was stopped. The chyloperitoneum regressed on the 5th day after surgery. In the demonstrated case, the NIRS monitoring made it possible to confirm the presence of hypoperfusion in real time and make a decision on the need for repeated surgery.

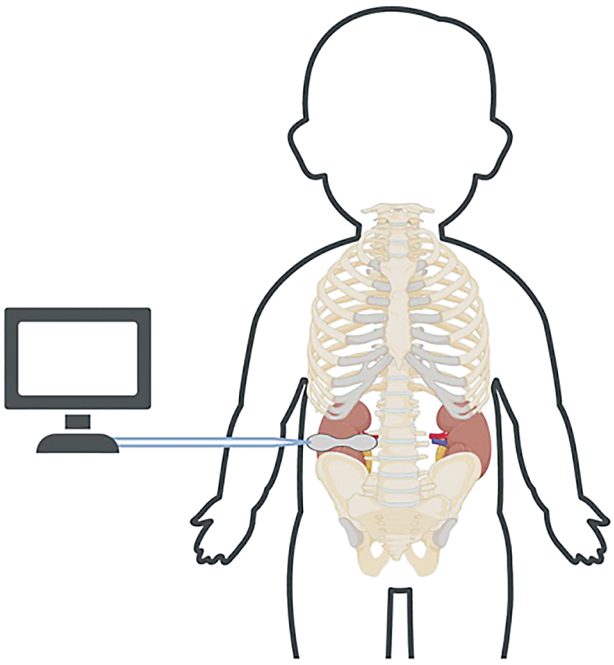

Fig. 1. Neonatal renal NIRS sensor location

Рис. 1. Расположение неонатального почечного датчика NIRS

Clinical case № 2

Boy B., 7 months old. Basic diagnosis: Congenital heart disease: hypoplastic left heart syndrome (mitral valve atresia, left ventricular hypoplasia, aortic valve atresia, aortic arch hypoplasia). The defect was diagnosed prenatally. On the 6th day of life, a modified Norwood operation (right ventricle — pulmonary artery) with a valve-containing bicuspidal alloconduit, atroiseptostomy under conditions of artificial circulation, antegrade cerebral perfusion and cardioplegia was performed. The course of the postoperative period was smooth and corresponded to the nature, volume and timing of the surgical intervention performed. At 1.5 months he was discharged home, the next stage of cardiac surgery was planned. At 5.5 months, a thrombosis of the alloconduit developed with severe myocardial ischemia, acute decompensation of chronic heart failure, a thrombolytic therapy was carried out with a positive effect. At 6 months, the Glenn's surgery was performed. In the early postoperative period, sinus

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tachycardia up to 160–170 beats per minute and a persistent increase in pressure in the cavapulmonary anastomosis (15–18 mm Hg) were noteworthy. An EchoCG revealed signs of dilatation of the right atrium against the background of regurgitation on the tricuspid valve of II–III degree. Despite the full conservative therapy, the child had a progressive clinical picture of retrograde pulmonary edema against the background of regurgitation on the tricuspid (systemic) valve and hypoperfusion of the abdominal organs, which was manifested by intolerance to enteral nutrition, severe dependence on high doses of loop diuretics to maintain an adequate pace diuresis. In order to assess the significance of regurgitation on the systemic valve and the accompanying hypoperfusion of the abdominal organs and kidneys over time, continuous extended NIRS monitoring of renal blood flow was initiated. Based on the monitoring results, the significant hypoperfusion was identified — average saturation values according to monitoring data were 43–45% lower than those according to transcutaneous pulse oximetry, average values were 33–37%, with regular episodes of desaturation up to 23–26% upon awakening and activation of the patient. Based on the totality of clinical and instrumental data, a decision was made to perform endovascular surgical intervention: a probing of the heart chambers, cardiac ventriculography, angiography of the great vessels. According to the results of the study, return angiopulmonograms show contrasting of the left atrium, contrasting of the pulmonary veins that flow into the left atrium is noted; the ventriculogram reveals regurgitation on the tricuspid valve of II–III degree, dilatation of the right atrium; Qp/Qs — 0.57/1. Based on the data obtained, a decision was made to replace the system valve. In this situation, in addition to the clinical picture and echocardiography data, confirmation of organ hypoperfusion using extended NIRS monitoring made it possible to make a decision to conduct an invasive study to determine further surgical tactics.

Clinical case № 3

Newborn boy, two days of life. Main diagnosis: Q23.4 Hypoplastic left heart syndrome (mitral valve hypoplasia, left ventricular hypoplasia, aortic valve hypoplasia, aortic arch hypoplasia). Fibroelastosis of the left ventricle. Coarctation of the aorta. Patent ductus arteriosus. Atrial septal defect. Ductus-dependent coronary and systemic circulation.

The pregnancy proceeded against the background of mild anemia, gestosis in the first half of pregnancy with hospitalization at 10/11 weeks. According to an ultrasound examination at 23/24 weeks of gestation, the congenital heart disease was detected: hypoplastic left heart syndrome. Micromelia? 1st urgent birth by emergency cesarean section due to severe preeclampsia at 39 weeks of gestation.

The child's condition at birth is satisfactory. Upon admission, the umbilical cord vein was catheterized and alprostan infusion was started. Noteworthy, there was moderate anemia, hemoglobin (145 g/l), probably caused by fetoplacental transfusion. At the end of the first day of life, a persistent high SpO2 was noted for this variant of the hemodynamics of the defect, which was in the range of 96–97%. According to the acid-base state, there was an increase in metabolic acidosis: BE = –9.5 mmol/l, HCO3 = 17.8 mmol/l, a decrease in the rate of diuresis to 0.8 ml/kg per hour was clinically noted. Clinical and laboratory data could indicate an imbalance of systemic and pulmonary blood flow, which is typical for patients with hypoplastic left heart syndrome, however, as a rule, its clinical manifestations occur on the 3rd–4th day of life, which is due to a decrease in pressure in the pulmonary circulation . To assess the adequacy of organ perfusion, the bedside NIRS monitoring of renal blood flow was initiated. According to the monitoring results, the absence of hypoperfusion was revealed — saturation according to monitoring data was 3–5% lower than the values according to transcutaneous pulse oximetry, average values were 87–90%, without episodes of significant desaturation. Based on the monitoring data, it was concluded that there was no imbalance in the pulmonary and systemic blood flow, hypoperfusion of the abdominal organs and kidneys, which was later confirmed by Doppler study. Taking into account the child's age and clinical and laboratory data, the red blood cell transfusion was performed according to individual selection. Against the background of correction of anemia, normalization of acid-base status indicators and a decrease in lactate levels to normal values were noted. Thanks to NIRS monitoring data, it was possible to refrain from early transfer to mechanical ventilation and sedation in order to limit pulmonary blood flow.

DISCUSSION

Adequate renal perfusion and oxygenation are critical to the outcome of critically ill neonates. At

the same time, in the routine practice of neonatal intensive care units, there are not enough diagnostic tools to assess the effectiveness of tissue oxygenation and blood flow, which, in turn, does not allow for the earliest and most reasonable therapeutic interventions aimed at preventing or reducing the degree of tissue damage.

In the presented clinical cases, the indicators of extended NIRS monitoring of organ blood flow correlated with the results of other instrumental studies. However, it should be noted that although the NIRS is a promising technology for monitoring organ blood flow in newborns and young children with congenital heart disease in the Intensive Care Unit, currently the number of multicenter randomized studies to determine the normative data of splanchnic oxygenation in young children, including in patients with hemodynamics of the same ventricle, very little.

G. Greisen et al. summarized the challenges of using tissue oximetry in an article discussing the prospect of introducing cerebral oximetry: "On the one hand, cerebral oximetry has the potential to become inexpensive because it is based on technology that can be mass-produced. Convincing evidence of benefit to patients will create a large market. On the other hand, what happens if the clinical application of cerebral oximetry is not developed in a rational, evidence-based format? This could then become another expensive technology applied randomly. Cerebral oximetry will be supported by anecdotal evidence, expert opinion, and aggressive branding and marketing. Consequences include unnecessary disruption and risks to a very vulnerable patient population and a drain on health care resources" [28].

One of the factors facilitating the widespread introduction of renal blood flow assessment by NIRS into clinical practice and the interpretation of the data obtained is the theoretical model of normal oxygenation of renal tissue in premature newborns during the first month of life (Fig. 2), proposed by M.W. Harer et al. (2020) based on publications by other authors, which reflects indicators of oxygen saturation of kidney tissue in the absence of pathology [29, 30].

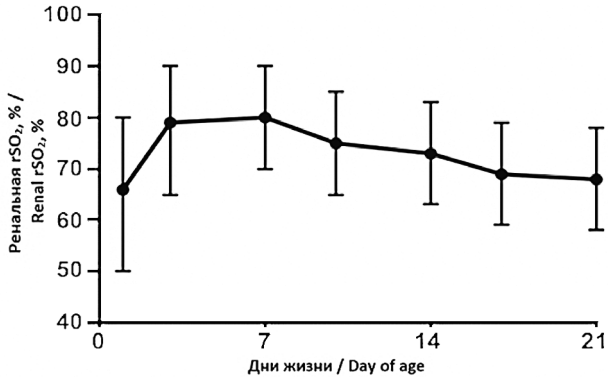

Fig. 2. Normal renal tissue oxygenation of premature newborns in the first month of life

Рис. 2. Показатели нормальной оксигенации тканей почек у недоношенных новорожденных в первый месяц жизни

CONCLUSION

The non-invasive real-time bedside monitoring of tissue oxygenation is a highly effective method for diagnosing disorders of organ perfusion and oxygenation and should be more widely used in neonatal intensive care units, especially in newborns with congenital heart disease.

ADDITIONAL INFORMATION

Author contribution. Concept and design of the study: Solovyova E.A., Trizna E.V.; collection and processing of primary material: Solovyova E.A., Romanova E.P.; writing the text of the article: Solovyova E.A., Pshenisnov K.V.; editing: Aleksandrovich Yu.S., Pshenisnov K.V., Trizna E.V. All authors read and approved the final version before publication.

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DYNAMICS OF MICROBIOME DEVELOPMENT IN A CHILD HOSPITALIZED IN THE INTENSIVE CARE UNIT FOR A LONG PERIOD OF TIME. CLINICAL CASE

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Abstract. The article presents the dynamics of microbiome development in a child hospitalized for a long time in the intensive care unit of a tertiary perinatal center. The species composition of the patient's microbiome did not meet the age norms. The risk factors that led to the disruption of microbiome formation were prolonged hospitalization in the NICU, short duration of breastfeeding, artificial nutrition with formulas based on deeply hydrolyzed cow's milk protein, and massive antibiotic therapy. Decrease in biodiversity of non-pathogenic microorganisms led to an increase in the proportion of pathogens, development of nosocomial diseases.

Key words: *microbiome formation; children; intensive care unit patient; 16s rRNA.*

ДИНАМИКА РАЗВИТИЯ МИКРОБИОМА РЕБЕНКА, ДЛИТЕЛЬНО ГОСПИТАЛИЗИРОВАННОГО В ОТДЕЛЕНИИ ИНТЕНСИВНОЙ ТЕРАПИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. В статье приводится динамика развития микробиома у ребенка, длительное время госпитализированного в отделение реанимации и интенсивной терапии перинатального центра третьего уровня. Видовой состав микробиома пациента не соответствовал возрастным нормам. К факторам риска, приведшим к нарушению формирования микробиома, относят длительную госпитализацию в отделение интенсивной терапии, короткую продолжительность грудного вскармливания, искусственное питание формулами на основе глубоко гидролизованного белка коровьего молока, массивную антибактериальную терапию. Снижение биоразнообразия непатогенных микроорганизмов привело к увеличению доли патогенов, развитию нозокомиальных заболеваний.

Ключевые слова: *формирование микробиома; дети; пациент отделения реанимации; 16s рРНК.*

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INTRODUCTION

Despite the presence of evidence of intrauterine development of the fetal microbiome, active colonization of microflora in children begins during the process of vaginal delivery (in utero) and continues after the birth of the child [1–4]. The microflora of parents, the environment and medical workers is of leading importance [5–12]. The method of delivery has an important role in the development of the microbiome: during natural delivery, representatives of the mother's vaginal microbiome (*Lactobacillus*, *Bifidobacterium* and *Bacteroides*) predominate, while during tomotocia, representatives of the skin microbiota (*Staphylococcus*, *Klebsiella* spp., *Enterococcus* spp. and *Clostridium* spp.) predominate [13–19].

The breast milk is of great importance in the development of gut microbiota, promoting the growth of *Lactobacillus* spp. and *Bifidobacterium* spp. [20–22]. In the first days after birth, the child's body begins to be colonized by representatives of *Enterobacteriaceae*, and then strict anaerobes: *Bifidobacterium*, *Clostridium* and *Bacteroides* [23–27]. *Bifidobacterium* are an essential component of a child's normal microflora; their development especially promoted by breastfeeding [28, 29]. The number of *Bacteroides* increases rapidly during the first 2–4 weeks of life [29]. During the weaning period, with the introduction of solid food, the abundance of *Bifidobacteriaceae* decreases, and *Bacteroides*, *Ruminococcus* and *Clostridium* predominate [30–32]. The microbiome of a child in the first few months of life characterized by a poor diversity of microorganisms [33]. It undergoes the greatest development with the introduction of complementary foods containing polysaccharides, which leads to the appearance of *Lachnospiracea*, *Clostridiaceae* and *Ruminococcaceae* and a sharp decrease in *Bifidobacterium* [3, 18, 34].

A disruption of the stages of development of the child's microflora in general and the intestines in particular can lead to the development of complications in various organs and systems [28, 35–39], and can also affect the prognosis [15, 40–42]. Children hospitalized in intensive care units from birth are susceptible to microbiome developmental disorders, which must be taken into account when providing medical care [43–51].

In order to demonstrate the detailed dynamics of changes in the microbiome of a child who was in the intensive care unit for a long time, we present our own observation.

CLINICAL CASE

A clinical case of a 10-month-old child, who was hospitalized from birth and was in the intensive care unit of a third-level perinatal center, was presented. The diagnosis is:

- Main disease: Non-epileptic paroxysms. Perinatal mixed damage to the central nervous system (CNS), early recovery period.
- Complications of the underlying disease: Movement disorder syndrome. Hyperkinetic syndrome. Bulbar syndrome. Delayed psychomotor development. Compensated biventricular occlusive hydrocephalus, a condition after ventriculoperitoneal shunting on the right.
- Concomitant diseases: Congenital malformation of the central nervous system — spina bifida, spinal hernia of the sacral spine, condition after plastic surgery. Microsurgical plastic surgery of myelomeningoradiculocele (rachischisis) of the sacral spine using local tissues. Arnold–Chiari syndrome type II. External ventricular drainage on the right under stereotactic ultrasound navigation. Distal paraparesis without dysfunction of the pelvic organs.
- Complications: Carrier of tracheostomy, gastrostomy. Stomach bleeding (3 episodes). Atopic dermatitis.

Anamnesis vitae. A child from the fourth pregnancy, which occurred against the of gestosis of the first half. The mother, 29 years old, was observed in the antenatal clinic from 21/22 weeks. During an examination of the mother at 27/28 weeks, positive IgG to rubella was detected (she had not previously had rubella, she was vaccinated). According to an ultrasound examination of the fetus at 36/37 weeks of gestation, a congenital malformation of the central nervous system of the fetus was diagnosed — spina bifida, occlusive hydrocephalus, Arnold-Chiari syndrome type II. In the area of the sacral region, a spinal defect with a hernial protrusion was visualized; the dimensions of the hernial sac were 27 × 10 mm, the diameter of the defect was 41 mm. During an ultrasound examination of the fetal head, the lateral ventricles are dilated to 23 mm, the anterior horns — to 24 mm. The cerebellum is displaced caudally.

Previous pregnancies ended in the birth of healthy children (2014, 2016, 2017). This birth was urgent at the 38th week by caesarean section in the lower segment of the uterus in a specialized perinatal center. The amniotic fluid was light.

Objective status at birth. At birth, the child's body weight was 3280 g, body length was 53 cm, head circumference was 36 cm, chest circumference was 34 cm. The Apgar score in the first minute was 7 points, in the fifth minute — 8 points. The child's condition at birth was assessed as severe due to the underlying disease—identified combined malformations of the central nervous system. At birth, a cry of medium strength, short-lived, against the background of tactile stimulation and sanitation of the upper respiratory tract. The head is round in shape. The large fontanel 1.0×1.0 cm, normotonic; the small fontanelle 0.3×0.3 cm, sutures at the junction. A spontaneous motor activity is symmetrically reduced. A muscle tone is symmetrical and semiflexor. The skin is bright pink, clean, acrocyanosis. The telangiectasia on the forehead. Visible mucous membranes are pink, moist, clean. Heart sounds are clear, rhythmic, no noise is heard, heart rate is 152 beats per minute. The breathing is symmetrical, weakened, vesicular, without wheezing, respiratory rate — 54 per minute, transcutaneous blood oxygen saturation — 97%. The abdomen is soft, not swollen, accessible to palpation. The liver protrudes from under the lower edge of the costal arch by 1.5 cm, the edge is smooth, elastic, the spleen is not palpable. The genitals are formed according to the male type, the testicles are lowered into the scrotum. No abdominal or femoral hernias were detected. Didn't urinate, anus closed. The meconium did not pass. In the lumbosacral region, there was a violation of the integrity of the skin and a hernial protrusion of myelomeningoradiculocele (rachischisis) measuring 5.5×7.0 cm with the flow of cerebrospinal fluid.

On the first day of life, an emergency surgical intervention was performed involving microsurgical plastic surgery of the myelomeningoradiculocele of the sacral spine using local tissues. The early postoperative period was uneventful. Due to increasing ventriculomegaly, on the 6th day of life, a diagnostic and unloading ventricular puncture was performed (cerebrospinal fluid without pathology). On the 8th day of life, due to increasing ventriculomegaly, emergency surgery was performed using external ventricular drainage on the right under stereotactic ultrasound navigation. The early postoperative period was without any features, respiratory support for two days using invasive artificial ventilation, analgosedation was continued, after that there was a planned transfer to spontaneous breathing, without any features, then without the need for respiratory support. During postoperative observation of the patient, no seizures or focal neurological symptoms were noted. The child was hemodynamically stable, did not require inotropic support. Enteral nutrition with expressed breast milk and physiological formula for children from birth with expansion up to 70 ml, absorbed. Due to an improvement in his condition, at the age of 11 days, the child was transferred to a specialized department, where the observation, treatment, nutrition were carried out with a gradual increase in the volume of enteral feeding.

From the 22nd day of life, a deterioration in the child's condition was noted in the form of the appearance and increase in the dynamics of bulbar disorders, hypersalivation, and an increase in respiratory failure; the child was transferred to the intensive care unit (ICU). Against the background of the child's anxiety, hyperdrainage was noted, against which background the development of general cerebral neurological symptoms was observed, migration of the drainage into the brain parenchyma was detected, and therefore the drainage was tightened under ultrasound navigation. According to control blood tests, an increase in laboratory inflammatory activity was noted (an increase in C-reactive protein to 33 mg/L), and therefore a control study of the cerebrospinal fluid was carried out — cytosis was detected up to 627 thirds. According to a bacteriological examination of blood and feces, carried out routinely as part of bacteriological control, E. coli was detected, and therefore antibacterial therapy was started based on sensitivity with control of bacterial cultures.

On the 23rd day of life, there was a decrease in saturation to 48%, bradycardia with a heart rate of up to 58 beats per minute, severe pallor of the skin, with diffuse cyanosis, focal neurological symptoms and dysphagia persisted. In this regard, an enteral nutrition was canceled, and the child was transferred to total parenteral nutrition.

At the age of 1 month, surgical intervention was performed to remove the external ventricular drainage on the right and implantation of the external ventricular drainage on the right.

On the 45th day of life, a repeated decrease in saturation to 45–60% was revealed during sleep, which was repeated several times; restoration of consciousness occurred after tactile stimulation. Due to persistent dysphagia, enteral nutrition was administered through a nasogastric tube and was completely absorbed. Similar episodes of desaturation due to apnea were observed on the 56th day. In this regard, the patient was transferred to invasive artificial lung

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ventilation (ALV) through an endotracheal tube, and anticonvulsant therapy was prescribed.

From the age of three months, given the developed atopic dermatitis, the patient was switched to formulas based on deeply hydrolyzed cow's milk protein.

Taking into account dysphagia and prolonged insertion of the tube, the boy was installed with a percutaneous endoscopic gastrostomy at 4,5 months age.

During the therapy, the child's condition remained severe due to respiratory failure of the I–II degree against the background of aspiration pneumonia, neurological symptoms: bulbar syndrome, paroxysmal nonepileptic seizures with desaturation and autonomic disorders, a syndrome of motor disorders, flaccid distal paraparesis without dysfunction of the pelvic organs, hyperkinetic syndrome.

Attempts at extubation and transfer to spontaneous breathing were unsuccessful, and therefore at 5,5 months age a tracheostomy was performed and mechanical breathing was continued. During observation, cough and swallowing reflexes were absent.

At 5,5, 6,5 and 7,5 months of age, episodes of gastrointestinal bleeding were recorded against the background of erosive esophagitis, superficial widespread gastritis and duodenal bulb ulcer.

The planned change of the tracheostomy cannula was carried out at 6,5 months age, and the gastrostomy tube — at 8 months age.

Results of changes in the patient's microbiome

The patient in the ICU during hospitalization periodically collected biological material (urine, feces, venous blood, tracheostomy discharge, gastric contents, swabs from the oropharynx and nasal cavity). At the age of 8,5 months, 16S rRNA sequencing of saliva, gastrostomy fluid and feces was performed. All isolated bacteria were identified by genus and species. 20 species of microorganisms have been identified, which are grouped into 3 bacterial phyla, 2 classes, 4 orders, 13 families and 15 genera.

When sequencing biological media, 3 bacterial phyla were identified: Firmicutes (represented by *Clostridium* spp., *Blautia* spp., *Lactobacillus* spp., *Enterococcus* spp., *Veillonella* spp., etc.), Proteobacteria (represented by the family *Enterobacteriaceae*), *Bacteroidota* (represented by *Elizabethkingia meningoseptica*). The dominant number of microorganisms contains the order *Proteobacteria* (65%), *Firmicutes* (32%) and *Bacteroidota* (3%). Sequencing analysis of numerous phyla *Proteobacteria* showed the presence of *Enterobacter* (41,068607), *Enterococcus* (31,280665) in large numbers.

Table 1. Summary of oral microflora data by culture and culturing method

Таблица 1. Суммарные данные микрофлоры ротовой полости культуральным методом и методом культивирования

Microorganisms	Oropharyngeal culture data	
	7 months	8,5 months
Streptococcus viridans	2	3
Serratia marcescens	0	2
Pseudomonas aeruginosa	0	2
Enterococcus faecalis	1	0

The cultivation of the contents of the oral cavity showed the presence of *Streptococcus viridans*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*. At the same time, an increase in the species diversity of pathogenic microflora in the oral cavity was noted (Table 1).

When sequencing a saliva sample, 300 OTUs were identified, which, in accordance with modern prokaryotic nomenclature, are divided into 8 bacterial phylum, 10 classes, 18 families, 22 genera and 27 species bacteria. The most pathogenic microorganisms isolated by sequencing from the oral cavity are Haemophilus influenzae, which may contribute to the development of aspiration pneumonia.

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Features of development gastrostomy microbiome

When sequencing a gastrostomy sample, 300 OTUs were identified, which, according to the modern nomenclature of prokaryotes, are divided into 7 bacterial phyla, 9 classes, 25 families, 38 genera and 34 species of bacteria. The equencing of gastrostomy fluid revealed 6 different phyla of bacteria and 1 unidentified phylum (Table 2, Fig. 1).

Table 2. Type diversity of the gastrostomy microbiome according to sequencing data

Таблица 2. Типовое разнообразие микробиома гастростомы по данным секвенирования

Microorganisms	Phylum	Ratio,%
Proteobacteria	76,88726	77
Cyanobacteria	21,001	21
Firmicutes	1,474338	1
Bacteroidota	0,515464	1
Fusobacteriota	0,077597	0
Actinobacteriota	0,033256	0
Unclassified	0,011085	0

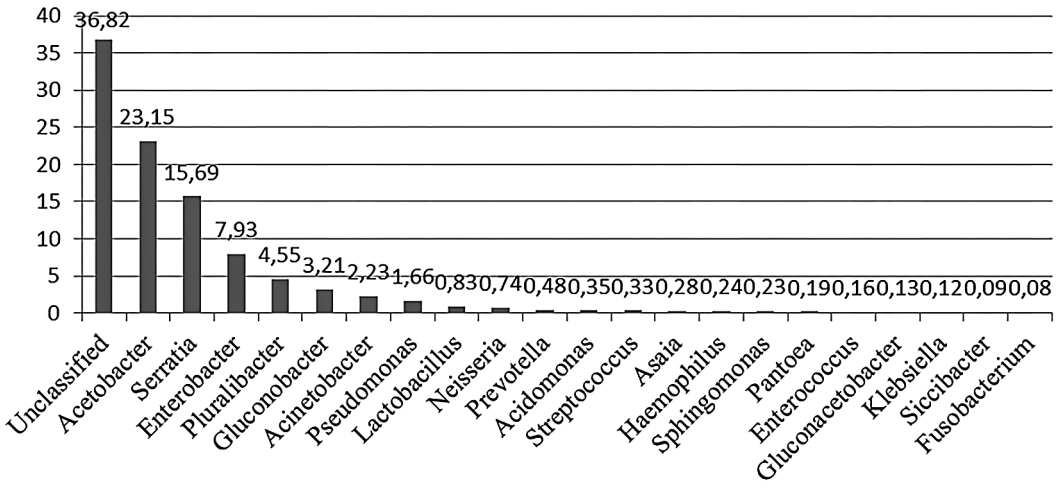

Fig. 1. Diversity of genera of the gastrostomy microbiome (%)

Рис. 1. Разнообразие родов микробиома гастростомы (%)

Table 3. Comparative composition of Genus 16S rRNA from stools

Таблица 3. Сравнительный состав Genus 16S rRNA из стула

Microorganisms	Class	Ratio,%	Microorganisms	Class	Ratio,%
Acinetobacter	0,04158		*Kluyvera*	0,00832	0
Anaerococcus	3,60915	4	*Morganella*	4,92308	5
Atlantibacter	0,01247	0	*Pseudocitrobacter*	0,02495	0
Cedecea	0,00832	0	*Raoultella*	0,56549	1
Citrobacter	2,75676	3	*Serratia*	0,59044	1
Enterobacter	41,0686	41	*Shimwellia*	0,19543	0
Enterococcus	31,2807	31	*Siccibacter*	0,00832	0
Escherichia/Shigella	5,40125	5	*Streptococcus*	0,01663	0
Klebsiella	2,17048	2	*Unclassified*	7,31809	7

Features of the development of the gut microbiome

The stool study was carried out using the culture method and the 16S rRNA method. The use of the cultural method for stool analysis showed the presence of 6 types of microorganisms: *Candida* sp., *Escherichia coli*, *Citrobacter* sp., *Enterobacter* sp., *Morganella morganii*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterococcus* sp. Microorganisms did not have a clear pattern of appearance in the stool throughout the patient's entire stay in the ICU.

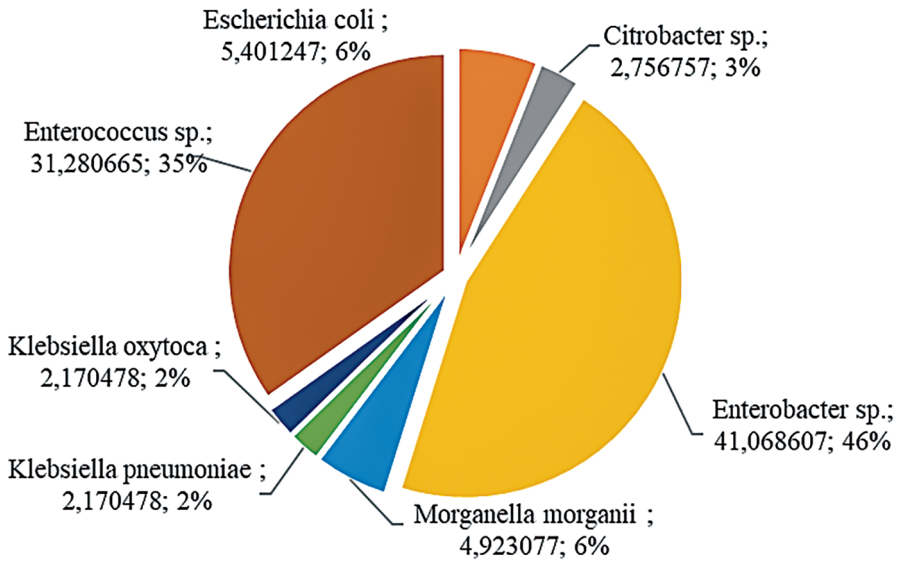

Fig. 2. Ratio of bacterial genera represented in fecal matter by 16S rRNA data

Рис. 2. Соотношение родов бактерий, представленных в каловых массах по данным 16S rRNA

Table 4. Comparative composition of Phylum 16S rRNA from oral cavity, gastrostomy and stools

Таблица 4. Сравнительный состав Phylum 16S rRNA из ротовой полости, гастростомы и стула

Phylum	Oral cavity	Contents of the gastrostomy	Stool microbiome
Firmicutes	48,69559	1,474338	37,75468
Proteobacteria	40,86186	76,887263	62,24532
Bacteroidota	7,979071	0,515464	0
Fusobacteriota	2,201875	0,077597	0
Patescibacteria	0,181673	0	0
Actinobacteriota	0,029068	0,033256	0
Unclassified	0,029068	0,011085	0
Campilobacterota	0,021801	0	0
Cyanobacteria	0	21,000998	0

When sequencing a stool sample, 274 OTUs were identified, which, according to the modern nomenclature of prokaryotes, are divided into 2 bacterial phyla, 4 classes, 19 genera and 17 species of bacteria (Table 3). The Biodiversity Index is 1,3118. Butyrate- and propionate-producing bacteria are practically absent in the feces of a child.

A comparison of two methods of stool analysis showed the presence of 7 identical genera of bacteria that had pathological activity (Fig. 2).

A generic comparison of microorganisms identified by stool sequencing revealed a significant predominance of Enterobacter (46%) and Enterococcus (35%). A large number of pathogenic strains associated with the provision of medical care were identified: 6% — Morganella morganii, 3% — Citrobacter sp., 2% — Klebsiella pneumoniae and 2% — Klebsiella oxytoca. Based on the data obtained, it can be assumed that these microorganisms contributed to the development of nosocomial infection (Table 4).

A comparative analysis of biological media obtained by sequencing showed that Firmicutes are present in three media, but the largest number of them is observed in the contents of gastrostomy tubes (48.69559) and stool samples (37.75468). The Proteobacteria occurs across the three environments, being the most abundant phylum. The largest number of phyla of microorganisms was isolated from the oral cavity.

In addition to 16S rRNA and cultivation, data from laboratory studies over time was analyzed.

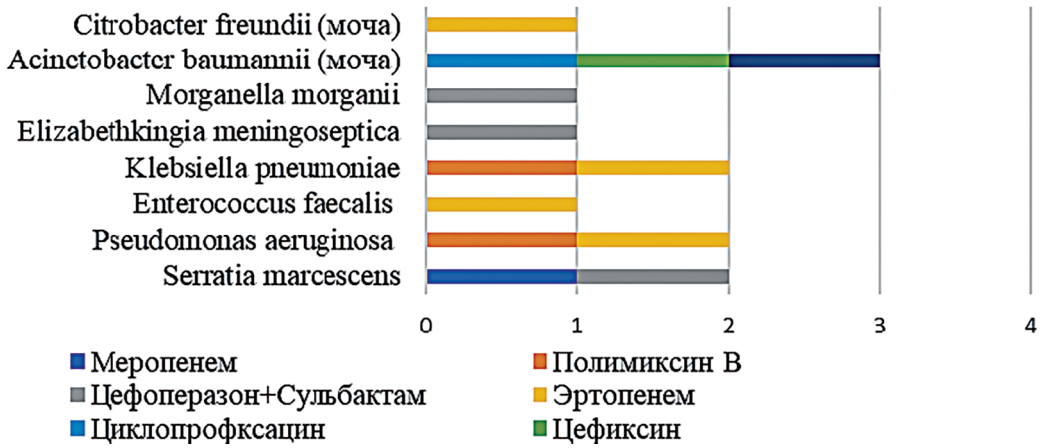

Fig. 3. Sensitivity of microorganisms to antibiotics

Рис. 3. Чувствительность микроорганизмов к антибактериальным препаратам

Throughout the entire period of treatment in the ICU, the patient observed a decrease in the concentration of total bilirubin, increased C-reactive protein in a biochemical blood test, eosinophilia and leukocytosis in a clinical analysis, which indicated the course of an inflammatory reaction.

Based on the dynamics of the increase in C-reactive protein, a positive procalcitonin test and the results of bacteriological studies, the patient was given antimicrobial therapy. The therapy with 10 antibacterial drugs selected according to sensitivity to specific pathogenic microorganisms was carried out during 8 months (Fig. 3).

DISCUSSION

Studies of different authors give an idea that the amount of Proteobacteria depends on the type of nutrition of the child: higher levels of phyla content are observed in children who are breastfed. It is also emphasized that, depending on nutrition, there is a different ratio of bacterial genera. Thus, with artificial feeding there is a predominance of *Clostridium difficile*, *Bacteroides* spp., *Prevotella* spp. and *Lactobacillus* spp. [1, 3, 29].

The smallest phylum isolated from the patient is *Bacteroidota* (3%), represented by *Elizabethkingia meningoseptica*. This species was isolated by cultivating bacteria from the contents of a gastrostomy tube. Considering the pathogenic properties of the microorganism, when it was isolated, treatment was carried out with antibacterial drugs of the reserve group (cefoperazone and sulbactam), against which positive dynamics were noted.

A detailed assessment of the bacterial phylum of the oral microbiome revealed 49% of unclassified microorganisms; among the classified ones, 49% belonged to *Firmicutes*, 41% to *Proteobacteria*, 8% to *Bacteroidota* (Fig. 1). Among the genera, the dominant ones were *Streptococcus* (29,55454), *Neisseria* (19,758738) and *Haemophilus* (18,828574). When examining the contents of the gastrostomy tube, microorganisms of 38 genera of bacteria were identified, the predominant of which were bacteria of the genus *Acetobacter* (23,14599) and *Serratia* (15,69117), which indicates the development of nosocomial infection. This fact is confirmed by other microorganisms present in the sequencing results: the genera *Acinetobacter* (2,228134), *Neisseria* (0,737169), *Pseudomonas* (1,657244).

In the species composition, *Lactobacillus* (0,825851) was identified in small quantities. They have immunomodulatory and anti-inflammatory effects and are involved in glucose metabolism [3]. Breastfed babies have a large number of bacteria. The patient was, firstly, artificially fed with formulas based on deep hydrolysis of cow's milk protein, and, secondly, received massive antibacterial therapy.

It was found that normal microflora predominated in the feces, represented by *Enterobacter* (41,0686), *Enterococcus* (31, 2807). However, pathogenic *Escherichia/Shigella species* (5,40125) have been observed, which should not normally be present in infants. Based on this, we can assume the development of pathogenetic processes in the child's gastrointestinal tract [33].

It was noted that the microbiota of the studied child does not differ in a large variety of microorganisms, as evidenced by the results of 16S rRNA sequencing.

CONCLUSION

The composition of the microbiome of a child hospitalized for a long time in the ICU does not correspond to age standards. Long stays in the ICU, short duration of breastfeeding and the transition to artificial nutrition with formulas based on deeply hydrolyzed protein led to poor microbiological diversity of the intestinal tube. The long-term massive antibacterial therapy with broad-spectrum drugs led to a decrease in the biodiversity index of microorganisms and a decrease in the number of bacterial colonies producing short-chain fatty acids.

Thus, the method of birth, type of nutrition, and use of antimicrobial drugs have a significant impact on the formation of the child's normal microflora.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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CLINICAL CASE OF A PATIENT WITH DISTAL RENAL TUBULAR ACIDOSIS WITH HEARING LOSS

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Abstract. Distal renal tubular acidosis with deafness (OMIM 267300) is a rare disease characterized by severe metabolic acidosis due to impaired excretion of hydrogen ions in the distal nephron. Violation of physical and psychomotor development, deformation of limbs, electrolyte disturbances without proper and timely treatment can lead to disability at a very early age. The article describes a clinical case that reflects the complexity and insidiousness of diagnosing distal renal tubular acidosis in a child of the first year of life.

Key words: *distal renal tubular acidosis; children; tubulopathy; sensorineural hearing loss.*

КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПАЦИЕНТА С ДИСТАЛЬНЫМ РЕНАЛЬНЫМ ТУБУЛЯРНЫМ АЦИДОЗОМ С ТУГОУХОСТЬЮ

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Резюме. Дистальный ренальный тубулярный ацидоз с глухотой (OMIM 267300) — это редкое заболевание, характеризующееся тяжелым метаболическим ацидозом вследствие нарушения экскреции водородных ионов в дистальном отделе нефрона. Нарушение физического и психомоторного развития, деформация конечностей, электролитные нарушения без должного и своевременного лечения могут приводить к инвалидизации уже в самом раннем возрасте. В статье описан клинический случай, отражающий сложность и коварность диагностики дистального ренального тубулярного ацидоза у ребенка первого года жизни.

Ключевые слова: *дистальный ренальный тубулярный ацидоз; дети; тубулопатия; нейросенсорная тугоухость.*

Distal renal tubular acidosis (DRTA) is a heterogeneous group of genetic diseases characterized by impaired urinary acidification, leading to severe metabolic hyperchloremic acidosis with elevated urinary pH, hypokalemia, hypercalciuria and nephrocalcinosis [1–3]. Clinical features include delayed height and weight, rickets, nephrocalcinosis, polyuria, polydipsia and the possible development of chronic renal failure in patients not receiving therapy [4–7].

There are primary and secondary causes of the development of distal renal tubular acidosis. Primary diseases include genetically determined pathology of transport systems with an autosomal dominant or autosomal recessive type of inheritance.

- Autosomal dominant, mutation of the *SLC4A1* gene (chromosome 17q21-22), disruption of the structure of chloride-bicarbonate antiporter-1 (AE-1 — anion exchager 1) of the basolateral membrane of the cortical collecting ducts.
- Autosomal recessive with hearing loss, mutation of the *ATP6V1B1* gene (chromosome 2p13), disruption of the structure of the B1 subunit of the hydrogen ATPase of intercalary cells of population A of the apical membrane of the cortical collecting ducts.
- Autosomal recessive without hearing loss, mutation of the ATP6V0A4 gene (chromosome 7q33-34), encoding the alpha-4 subunit of the hydrogen ATPase of intercalary cells of population A of the apical membrane of the cortical collecting ducts [1, 2, 4].

Autosomal recessive forms of distal renal tubular acidosis are rare diseases with unknown prevalence in the population [7]. The presence or absence of hearing impairment is the main phenotypic criterion to narrow the genetic search to confirm the diagnosis. Causal mutations in the ATP6V1B1 gene are classically associated with early-onset sensorineural hearing loss, but cases of tubular acidosis with early-onset deafness have also been described in patients with ATP6V0A4 gene mutations. Along with familial forms of the disease, sporadic cases are also found.

Secondary (acquired) forms of distal RTA are described in many pathological conditions caused by disorders of calcium metabolism with nephrocalcinosis and hypercalciuria, primary hyperparathyroidism, drug and toxic damage, other renal diseases, including medullary cystic disease and sponge kidney, autoimmune diseases (hypergammaglobulinemia, Sjogren's syndrome, autoimmune hepatitis, thyroiditis, fibrosing alveolitis, systemic lupus erythematosus, periarteritis nodosa).

The violation of ammonium excretion in all cases is secondary. A bicarbonate reabsorption is quantitatively normal, but, consistent with the increase in urine pH, a certain degree of bicarbonaturia is necessarily present. In severe chronic metabolic acidosis, the neutralization of hydrogen ions occurs due to bone carbonate, which causes the release of calcium from the bone into the extracellular fluid, which leads to disruption of its normal structure and a variety of bone deformities. A citrate excretion in the proximal tubule is reduced, which is the basis for the formation of nephrocalcinosis.

CLINICAL PICTURE OF DISTAL RENAL TUBULAR ACIDOSIS

The disease more often manifests between the age of six months and two years. Usually the DRTA is characterized by nonspecific symptoms: delayed weight and height, rachitic-like skeletal changes, muscle hypotonia, polyuria, polydipsia.

LABORATORY AND INSTRUMENTAL METHODS FOR DIAGNOSIS OF DISTAL RENAL TUBULAR ACIDOSIS

Blood acid-base state. One of the main criteria for laboratory diagnosis is the identification of metabolic acidosis, due to a decrease in standard bicarbonate (HCO3–) in plasma < 15 mmol/l.

Urine analysis. The most characteristic is an alkaline reaction of urine (pH > 6.0); a decrease in the excretion of citrate and ammonium is also possible [3].

Biochemical blood test. Changes in blood chemistry for DRTA are nonspecific, but increases in alkaline phosphatase, parathyroid hormone, renin, and aldosterone levels may occur.

Genetic research. For the distal renal tubular acidosis, an autosomal dominant type of inheritance with a mutation in the *SLC4A1* gene (chromosome 17q21-22), as well as autosomal recessive types with a mutation in the *ATP6V1B1* (chromosome 2p13) and *ATP6V0A4* genes (chromosome 7q33-34) are possible.

Ultrasound. The distal renal tubular acidosis is characterized by echo signs of nephrocalcinosis ("hyperechoic pyramid syndrome") according to the results of ultrasound of the kidneys, as well as urolithiasis (the composition of urinary stones is calcium phosphate) [1, 2].

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In order to assess the severity of rachitic changes in the skeleton, it is recommended to conduct X-ray of the hands, determine bone age, densitometry, and X-ray of the tubular bones of the legs including the knee joints.

DIFFERENTIAL DIAGNOSTICS

Genetically determined forms of distal RTA (type I) must be differentiated from proximal RTA (type II), including those in the de Tony-Debre-Fanconi composition syndrome, pseudohypoaldosteronism, primary hyperoxaluria and some other variants of nephrocalcinosis.

TREATMENT OF DISTAL RENAL TUBULAR ACIDOSIS

According to clinical recommendations [1, 2], treatment of RTA II in children consists of using a 4% sodium bicarbonate solution or a citrate solution at a dose of 10–15 mmol/kg per day in several doses to compensate for metabolic acidosis.

Since untimely diagnosis of the disease significantly worsens the quality of life of patients, and in some cases can cause death, the team of authors considers it necessary to pay the attention of colleagues to the presence of such a pathology as distal renal tubular acidosis, and presents a description of a clinical case.

CLINICAL CASE DESCRIPTION

Patient V., 4 months old, was admitted for the first time as planned to the nephrology department of St. Petersburg State Budgetary Healthcare Institution Children's City Hospital № 2 of St. Mary Magdalene.

Anamnesis morbi. A screening ultrasound of the urinary system at 2 months revealed echo signs of nephrocalcinosis ("hyperechoic pyramid syndrome"). At 4 months bilateral sensorineural hearing loss was detected: degree III on the right, degree IV on the left.

Anamnesis vitae. A child from the third pregnancy, third birth. Labor at 39 weeks, Apgar score 8/9. Body weight at birth was 3560 g, body length was 53 cm. The mother suffered a new coronavirus infection (COVID-19) and received a course of nasal glucocorticosteroids at the 8th week of pregnancy. Heredity, according to the mother, is not burdened. The elder children (boy — 8 years old, girl — 4 years old) are healthy.

Objective examination data upon admission to the hospital. The body length was 62 cm, body weight was 5500 g. The condition is satisfactory. A psychomotor development corresponds to age. The skin is naturally colored and clean. There was insufficiently of subcutaneous fat layer. A hypotonia of the lower extremities is noted. Heart sounds are clear and rhythmic. In the lungs, breathing is puerile, carried out in all sections. There was no wheezing. The abdomen is moderately swollen, accessible to deep palpation. The liver is + 1,5 cm from under the edge of the costal arch. The spleen is not palpable. The stool is mushy, 3–4 times a day, without pathological impurities. The urination is freely into the diaper.

Data from laboratory and instrumental examination methods.

The clinical blood test is in the age norm. No evidence of mineral metabolism disorders was identified (blood electrolytes are normal; urine calcium/creatinine, phosphorus/creatinine ratios are within normal limits). A general urine test revealed an alkaline reaction, without changes in urinary sediment. No disturbances in the acid-base status (ABS) of the blood were detected. The hormonal profile showed a decrease in the level of parathyroid hormone to 9,63 pg/ml, an increase in the level of renin (> 500.00 μIU/ml, reference values for renin for children under 1 year of age have not been established) and an increase in the level of aldosterone to 935,3 pg/ml , without clinical manifestations. The thyroid status, 17-OH-progesterone is normal. A nitrogen excretion function of the kidneys is satisfactory. A blood pressure is within target values.

An ultrasound of the urinary system showed echo signs of "hyperechoic pyramid syndrome", without negative dynamics.

The child was consulted by an endocrinologist; no evidence of endocrinological pathology was found at the time of examination. Then he consulted by a geneticist: taking into account bilateral sensorineural hearing loss, blood was drawn to study the mutation in the GJB2 gene and blood amino acids — in work at the time of discharge.

The child was discharged with the main diagnosis; nephrocalcinosis, and concomitant: bilateral sensorineural hearing loss — degree III on the right, degree IV on the left. The dynamic observation and control examination after 3 months were recommended.

A repeated hospitalization in August 2022. At the time of hospitalization, the child was 10 months old. The llow weight and height gains were observed over time. The hearing replacement was performed at 6 months.

Since July 2022, a polydipsia and polyuria have been noted. During control studies, the level of adrenocorticotropic hormone (ACTH) and aldosterone remained elevated. According to repeated monitoring, no electrolyte disturbances were detected. In urine tests over time, a persistent shift in urine pH towards the alkaline side is noted. When monitoring blood pressure, episodes of blood pressure increases up to 110/60 mmHg were recorded. According to the results of a genetic examination (from January 2022), disorders of amino acid metabolism were excluded, mutations in the GJB2 gene were excluded. Hearing correction was performed in 6 months age.

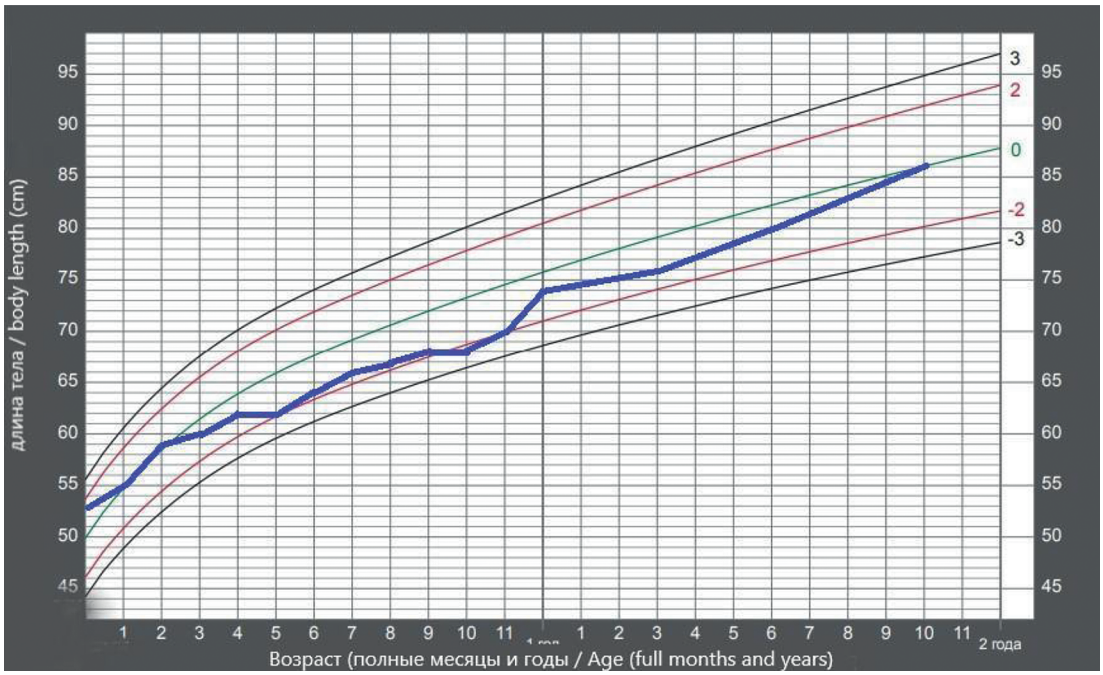

Fig. 1. Patient growth chart from birth to 22 months
Рис. 1. График динамики роста пациента от рождения до 22 месяцев

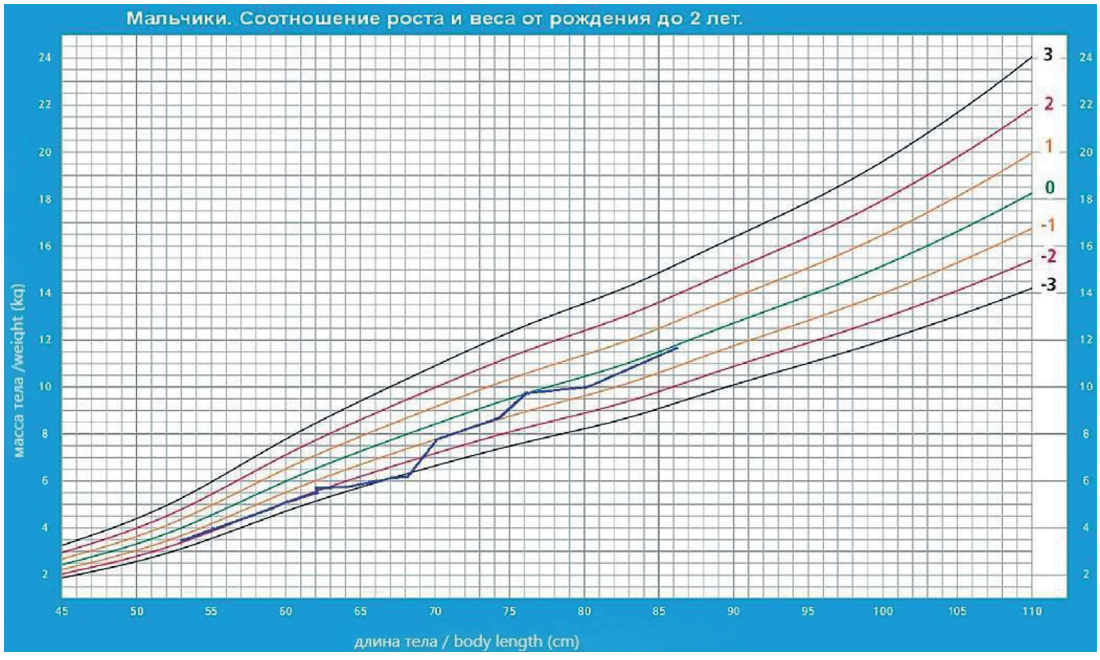

Fig. 2. The ratio of the patient's body length and body weight from birth to 22 months
Рис. 2. Соотношение длины тела и массы тела пациента от рождения до 22 месяцев

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Table 1. Laboratory indicators of the patient over time

Таблица 1. Лабораторные показатели больного в динамике

	Кислотно-основное состояние капиллярной крови / Acid-base state of capillary blood				
	01.2022	**08.2022**	**12.2022**	**03.2023**	**06.2023**
pH	7,45	7,30	7,43	7,46	7,43
Напряжение CO_2, мм рт.ст. / CO_2 tension, mmHg	46,6	21,5	32,4	33,3	34,6
Напряжение O_2, мм рт.ст. / O_2 tension, mmHg	65	84	78	77	69
Лактат / Lactate	–	2,43	–	–	–
Гематокрит, % / Hematocrit, %	39	33,0	33,0	–	36,0
Концентрация Na^+, ммоль/л / Na+ concentration, mmol/l	138	132	138	139	137
Концентрация K^+, ммоль/л / K^+ concentration, mmol/l	4,5	3,0	3,8	4,5	4,6
HCO_3^-, ммоль/л / HCO_3^-, mmol/l	32,4	10,5	21,6	23,7	23,1
cBase (B), ммоль/л / cBase (B), mmol/l	4	–14,0	–2,0	0	–1
$ctCO_2$ (B), ммоль/л / $ctCO_2$ (B), mmol/l	34	11,0	23,0	25,0	24,0
sO_2, %	93	95,0	96,0	96,0	94,0
	Общий анализ мочи / General urine analysis				
Кислотность / Acidity	Щелочная / Alkaline	Щелочная / Alkaline	Нейтральная / Neutral	Слабощелочная / Slightly alkaline	Нейтральная / Neutral
Удельный вес / Specific gravity	1025	1020	1018	1020	1015
Белок / Protein	0	0	0	0	0
Глюкоза / Glucose	0	0	0	0	0
Эпителий плоский / Flat Epithelium	2–3	0–1	1–2	2–3	1–2
Лейкоциты / Leukocytes	5–7	2–3	3–5	2–3	0–1
	Биохимический анализ крови / Biochemical blood test				
Ренин, мкМЕ/мл / Renin, μIU/ml	>500,00	>500,00		84	28
Альдостерон, пг/мл / Aldosterone, pg/ml	953,3	158,5		147,5	
Паратгормон, пг/мл / Parathyroid hormone, pg/ml	9,63	24,41		26,8	
Общий белок, г/л / Total protein, g/l	72	67	66	62	67
Альбумин, г/л / Albumin, g/l	53	46	43	42	45
Мочевина, ммоль/л / Urea, mmol/l	4,8	4,5	7,0	6,7	3,9
Глюкоза, ммоль/л / Glucose, mmol/l	6,2	4,9	4,6	4,8	3,8
Мочевая кислота, ммоль/л / Uric acid, mmol/l	200	157	165	183	248
Креатинин, мкмоль/л / Creatinine, μmol/l	29	27	25	27	30
Кальций общий, ммоль/л / Total calcium, mmol/l	2,.74	2,58	2,72	2,44	2,67
Фосфор, ммоль/л / Phosphorus, mmol/l	2.00	1.24	2,53	1.89	1.53
Железо, мкмоль/л / Iron, μmol/l	13.9	7.0	8,6	36	18.8
Ферритин, мкг/л / Ferritin, μg/l	56	54	12	6,3	
Калий, ммоль/л / Potassium, mmol/l	4.50	3.7	3.8	4,6	4.9
Натрий, ммоль/л / Sodium, mmol/l	135	132	138	137	139
Хлор, ммоль/л / Chlorine, mmol/l	107	107	109	106	108
Аспартатаминотрансфераза, Ед/л / Aspartate aminotransferase, U/l	36	40	24	28	
Аланинаминотрансфераза, Ед/л / Alanine aminotransferase, U/l	24	13	15	20	
Витамин D, 25-гидрокси (кальциферол), нг/мл / Vitamin D, 25-hydroxy (calciferol), ng/ml	31,32				
17-гидроксипрогестерон (17-ОПГ), нг/мл / 17-hydroxyprogesterone (17-OPG), ng/ml	0,85				

Objective examination data upon admission to the hospital. The height was 68 cm and weight was 6,1 kg (dynamics of physical development are presented in Fig. 1, 2). There is a delay in psychomotor development within two months (assessed using the Griffiths scale). The condition is satisfactory. The skin is naturally colored, dry, and there is a decrease in skin turgor. The subcutaneous fat layer is not sufficiently expressed in the abdomen and thighs. Muscular hypotonia (hypotonia of the lower extremities, "frog belly") is noted. Heart sounds are clear and rhythmic. SS at the top. In the lungs, breathing is puerile, carried out in all sections. No wheezing was detected. The abdomen is moderately swollen, accessible to deep palpation. The liver is at the edge of the costal arch. The spleen is not palpable. The stool is mushy, 1–2 times a day, without pathological impurities. The urination is freely into the diaper.

Data from laboratory and instrumental examination methods.

The clinical blood test is within the age norm. In the urine analysis, a shift in the pH of urine to the alkaline side. The urine Ca/Cr ratio is hypercalciuria. The urine P/Cr ratio is normal. Blood ABS is metabolic acidosis (data are presented in Table 1). Biochemical blood test shows hypokalemia. Kidney function is satisfactory. The level of cortisol, aldosterone, parathyroid hormone, ACTH is normal. A thyroid status — subclinical hypothyroidism. When monitoring hydrobalance, polydipsia is noted up to 1800 ml/day, polyuria up to 1900 ml/day. An ultrasound of the urinary system shows echo signs of "hyperechoic pyramid syndrome", without negative dynamics. Taking into account clinical and laboratory data (low height and weight gain, bilateral sensorineural hearing loss, nephrocalcinosis, persistent shift in urine pH to the alkaline side, metabolic acidosis, polydipsia, polyuria, hypercalciuria, hypokalemia), the diagnosis was interpreted as distal renal tubular acidosis with hearing loss. An exome sequencing has been carried out — in progress. In therapy, a citrate solution (blemaren at the rate of 5 mmol/kg per day for citrate), ACE inhibitor therapy (Enap 2,5 mg/day), against this background, in the 2nd week there was a normalization of ABS, blood electrolytes, a decrease in the volume of consumed and excreted liquids.

The third hospitalization was in October 2022, against the background of therapy with a citrate solution. The positive dynamics in weight and height indicators were noted, the data are presented in Fig. 1, 2.

The laboratory data at the time of hospitalization: capillary blood ABS, ionogram, biochemical and clinical blood tests were within the reference values (the results of laboratory data are presented in Table 1). A general urinalysis reveals a slightly alkaline urine reaction. Based on the results of exome sequencing, a heterozygous ATP6V1B1 mutation was identified, which confirms the previously made clinical diagnosis.

Readmissions in December 2022, March and July 2023. During each of the hospitalizations, compensation of metabolic acidosis was noted (laboratory data are presented in Table 1) and the absence of clinical manifestations, satisfactory weight and height indicators (Fig. 1, 2).

CONCLUSION

The diagnosis of tubulopathy, including renal tubular acidosis, is a rather difficult task for a pediatrician and nephrologist, since in practice it is quite difficult to establish the type of disease, the described clinical case proves this. Thus, taking into account clinical and instrumental data, including general signs of distal renal acidosis and the presence of nephrocalcinosis and sensorineural hearing loss in the boy, the clinical diagnosis of DRTA was confirmed genetically (heterozygous variant ATP6V1B1). A timely treatment started and leaded to compensation of metabolic acidosis with use of citrate solution, and timely hearing aids for the patient made it possible to prevent retardation of physical and psychomotor development.

ADDITIONAL INFORMATION

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

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ведение 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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GALACTOSEMIA TYPE I: A CASE FROM PRACTICE

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Abstract. Galactosemia is a hereditary disorder of carbohydrate metabolism, as a result of mutation of genes encoding enzymes involved in galactose metabolism. With late diagnosis and the absence of pathogenetically justified diet therapy, the disease can lead to multiple organ failure and death. The article presents the issues of pathogenesis, clinical manifestations, diagnosis and principles of dietary therapy of galactosemia in children. The author presents his own clinical observation, which highlights a complex example of differential diagnosis of galactosemia with intrauterine infection in a child in the neonatal period.

Key words: *galactosemia; clinical case; screening.*

ГАЛАКТОЗЕМИЯ I ТИПА: СЛУЧАЙ ИЗ ПРАКТИКИ

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Резюме. Галактоземия — наследственное нарушение обмена углеводов, возникающее в результате мутации генов, кодирующих ферменты, которые участвуют в обмене галактозы. При поздней диагностике и отсутствии патогенетически обоснованной диетотерапии заболевание может привести к полиорганной недостаточности и летальному исходу. В статье изложены вопросы патогенеза, клинических проявлений, диагностики и принципов диетотерапии галактоземии у детей. Представлено собственное клиническое наблюдение, где освещен сложный пример дифференциальной диагностики галактоземии с внутриутробной инфекцией у ребенка в неонатальном периоде.

Ключевые слова: *галактоземия; клинический случай; скрининг.*

INTRODUCTION

Timely diagnosis of congenital metabolic disorders in a newborn child remains a topical issue of pediatrics [1].

Galactosaemia is a hereditary disorder of carbohydrate metabolism that occurs as a result of mutation of genes encoding enzymes that are involved in galactose metabolism. As a result of these disorders, an excess of galactose and its metabolites (galactose-1-phosphate and galactitol) accumulates in the body, which determines the clinical picture of the disease and the formation of delayed complications.

The type of inheritance of galactosaemia is autosomal recessive. The incidence of the disease in the Russian Federation is 1:20 000, with the vast majority of cases of the disease caused by mutations in the GALT gene (classical galactosaemia type I).

The main carbohydrate component of breast milk and infant formula is lactose, a disaccharide

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consisting of two monosaccharides, galactose and glucose. Despite the great similarity between the molecules of glucose and galactose, the conversion of the latter into glucose requires several enzymatic reactions [2].

Galactosaemia combines several genetically heterogeneous forms. The disease is based on the deficiency of one of the three enzymes involved in galactose metabolism: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK) or uridine diphosphate (UDP)-galactose-4-epimerase (GALE). The abnormality of one of these enzymes is genetically caused by mutations in the genes encoding the protein structure of the enzyme molecule, leading to the synthesis of a defective enzyme and a significant decrease in its activity. As a result, the normal metabolism of galactose is blocked and a large number of toxic substances are formed (galactonate, galactitol, galactose-1-phosphate, etc.), which, along with galactose, accumulate in the blood and provoke the development of severe lesions of internal organs (liver, brain, kidneys), manifested by polymorphism of implictations [3–5].

Galactose is essential for the growth and development of the child's body. This monosaccharide is not only a source of energy for the cell, but also plays an important role as prebiotic, serving as a necessary plastic material for the formation of glycoproteins, glycolipids and other complex compounds used by the body to form cell membranes, nerve tissue, nerve endings, myelination of neurons, etc. The main source of galactose in humans is food. The large amount of food consumed during the day (primarily dairy) contains lactose, from which galactose is formed in the intestines as a result of hydrolysis [6].

There are three types of galactosaemia depending on the patient's defect of one of the three major enzymes involved in galactose metabolism:

- classical — galactosaemia type I, caused by deficiency of the GALT enzyme, includes the Duarte variant galactosaemia (decreased enzyme activity);
- galactosaemia type II — GALK deficiency;
- galactosaemia type III — GALE deficiency.

Classic galactosaemia manifests itself in the neonatal period during feeding with breast milk or infant formula. Manifestations of the disease may include abundant regurgitation, vomiting, diarrhea, lack of weight gain, lethargy, drowsiness, and later — signs of malnutrition, stunting and retardation of psychomotor development. In the absence of timely diagnosis and pathogenetically justified diet therapy, symptoms of liver disease appear and increase, accompanied by hypoglycemia, jaundice, hepatosplenomegaly, and hemorrhagic syndrome. In the neonatal period, patients with galactosaemia, due to the suppression of protective immune reactions, have an increased risk of developing sepsis caused by Escherichia coli (E. coli), which often leads to death. The disease progresses rapidly and in the absence of treatment is life-threatening.

Neonatal screening is recommended for all newborns to identify inherited disorders of galactose metabolism. Diagnostics is aimed at determining the concentration of total galactose in a dried blood spot; if the result is positive, the activity of the GALT enzyme and major mutations in the GALT gene are determined [4].

The main method of treating galactosaemia is diet therapy, which involves lifelong exclusion from the diet of products containing galactose and lactose. The patient should completely refrain from eating any kind of milk (female, cow, goat, infant formula, etc.) and all dairy products, as well as carefully avoid those products in which they can be added: bread, pastries, caramel, sweets, margarine, etc. The use of low lactose milk and infant formula is also prohibited. It should be taken into account that a number of products of plant origin contain oligosaccharides — galactosides (legumes (peas, beans, lentils, mung beans, chickpeas), soybeans (but not soy protein isolate), spinach, cocoa, chocolate, nuts), and in products of animal origin — glycoproteins (liver, kidneys, brains and other by-products), which under certain conditions can be split and be a source of galactose [3].

In the formulation of therapeutic diets for children in the first year of life with the disease, the amount of basic food ingredients and energy should be in accordance with age-specific physiological standards. Breast milk and/or infant formula should be replaced with lactose-free formulas adapted to their composition. To treat patients with galactosaemia, specialized infant formulas based on soy protein isolate (Bellakt Soya, Nutrilak Soya, Nutrilon Soya, Frisosoy) or extensively hydrolyzed whey are used — in case of allergy to soy protein. Formulas based on synthetic amino acids and lactose-free, casein-dominant infant formulas are also used. It is not recommended to use lactose-free whey protein-dominant baby formulas with a predominance of whey proteins (60% or more). These infant formulas may contain trace

amounts of galactose. Specialized infant formulas are introduced into the diet of patients with galactosaemia within one day, immediately after diagnosis. Patients are strictly recommended to introduce lactose-free complementary foods and a lifelong lactose-free diet.

It is not recommended for patients of any age to use medications containing lactose/galactose, as well as homeopathic remedies, tinctures and alcoholic drug forms. Thus, lactose is often used as an excipient in homeopathic medicines, and ethanol inhibits the elimination of galactose from the liver [3].

The outcome and course of the disease are influenced by the timing of diagnosis, timely and adequately prescribed diet treatment and emergency measures (transfusion of blood substitutes, infusion therapy). The prognosis of the disease is unfavorable in late-diagnosed severe forms of galactosemia (due to the lack of screening). With timely treatment, the prognosis for the life and development of patients is significantly improved.

AIM OF THE STUDY

The aim is to examine the clinical manifestations and differential diagnosis of the disease using the example of a particular patient with galactosaemia.

CLINICAL CASE

We present a case of observation of a patient with classical galactosaemia type I based on examination of a child, study of his medical history and outpatient card.

A 10-day-old girl with complaints of severe jaundice of the skin was admitted to the neonatal pathology department of the Republican Children's Clinical Hospital in Donetsk.

The child was born in the maternity hospital of Torez, Donetsk People's Republic. A child from the fourth pregnancy, flowing on the background of colpitis, polyhydramnios, and gestational hypertension. The mother suffers from nicotine dependence and continued to smoke during pregnancy. At 11 weeks, she was examined at the medical genetic center — no pathology was found. Fetal ultrasound was performed 3 times — no pathology was detected. Previous pregnancies: first pregnancy — normal delivery, second — miscarriage at 10 weeks, third — normal delivery. This delivery is the fourth, premature, at 36 weeks of dichorionic diamniotic twins, by cesarean section due to the transverse baby position. The child was born as the second of twins with a weight of 2300 g, length — 47 cm. Apgar score was 7–8 points. The child Screamed immediately. She was bottle-fed with expressed mother's breast milk. On the 2nd day of life, skin and scleral icterus appeared: total bilirubin — 205 μmol/l due to the indirect bilirubin. On the 9th day of life, total bilirubin was 388 μmol/l, direct bilirubin was 67.6 μmol/l.

For the first 9 days of life in the maternity hospital, the child received phototherapy, ursodeoxycholic acid preparations, bifidumbacterin, and vitamin D3 aqueous solution. There were no positive changes in the child's condition. On the 10th day of life, the child was transferred to the neonatal pathology department of the Republican Children's Clinical Hospital in Donetsk.

The general condition of the child on admission to the clinic is serious. There are symptoms of prematurity and immaturity. Newborn and spinal cord reflexes are depressed, and oral reflexes are evoked. Muscle tone is dystonic, spontaneous motor activity is reduced. Anterior fontanelle 3.0×4.0 cm, at the level of the skull bones. Natural feeding — expressed breast milk. Visible mucous membranes and skin are icteric and clean. Tissue turgor and skin elasticity are reduced. The subcutaneous fat layer is thinned. Peripheral lymph nodes are not enlarged. Above the lungs, on percussion is a normal pulmonary sound, auscultation is puerile respiration, wheezing is not heard. The boundaries of relative cardiac dullness are within the age norm. Heart sounds are muffled, rhythmic, systolic murmur over the entire area of the heart. The abdomen is palpable, symmetrical, increased in volume. Peristalsis is active. The liver is palpated at 4.0 cm below the costal margin. The kidneys and spleen are not palpable. The stool is mushy, yellow, mixed with mucus. Urine is dark yellow.

The child was examined in the department.

Complete blood count revealed mild anemia, which persisted over time, and an increased erythrocyte sedimentation rate (ESR).

Biochemical blood test on admission showed hyperbilirubinemia (total bilirubin up to 440 μmol/l, direct bilirubin — 175 μmol/l), elevated transaminase levels (aspartate aminotransferase (AST) — 109 U/l, alanine aminotransferase (ALT) — 67 U/l).

Coprocytogram: neutral fat + +, leukocytes — 8–10 in the field of view.

Stool, nasopharyngeal and umbilical wound culture — pathogens and opportunistic pathogens not detected.

Kidney ultrasound is normal.

Abdominal ultrasound: in the abdominal cavity between the liver and diaphragm, along the round ligament of the liver, as well as between the spleen, stomach and intestines, along the flanks, in the lesser pelvis free fluid with fibrin threads and finely dispersed suspension is determined. The peristalsis in small intestine is sluggish. The wall of the small intestine on the visualized fragment is thickened to 1.5 mm, there is liquid content in the lumen of the large intestine.

Neurosonography: echo signs of brain immaturity, hypoxic-ischemic brain injury; hemodynamics are not changed.

Consultation of neurologist: mild hypoxic ischemic encephalopathy of the 1st degree. Cortical excitation.

Consultation of ophthalmologist: consultation: bilateral cataract.

Based on the clinical picture and additional examination data, the child was suspected of having an intrauterine infection, hepatitis, enterocolitis against the background of prematurity and immaturity.

Received treatment: feeding with the Belakt, then Nutrilon, antibiotic therapy (cefipime, amikacin), 10% glucose solution, 0.9% NaCl solution, aminoven solution, calcium gluconate, ursodeoxycholic acid preparations, bifidumbacterin.

During screening at the medical genetic center, an increase in galactose to 90 mg/dc was noted; during the repeat study on the 16th day, the galactose level remained elevated to 66.33 mg/dc. The child was consulted by a geneticist and galactosaemia was diagnosed. Prescribed diet with the exclusion of galactose, lactose, and a transition to feeding an infant formula based on soy protein isolate.

It is recommended to dynamically examine the level of galactose, blood biochemistry test, and abdominal ultrasound.

During the telemedicine conference, the child was consulted at the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov. Based on the presented data, a late preterm infant has a clinical picture of galactosaemia.

Based on genetic molecular testing, the child has two mutations of the GALT gene — type I galactosaemia was diagnosed.

Biochemical blood test: triglycerides — 0.87 mmol/l, cholesterol — 3.69 mmol/l, alkaline phosphatase — 461 U/l, albumin — 34.0 g/l, calcidiol — 6.1 ng/ml, urea — 4.4 mmol/l, glucose — 2.9 mmol/l, protein — 60 g/l, creatinine — 27 μmol/l, calcium — 2.31 mmol/l, potassium — 4.3 mmol/l, sodium — 142 mmol/l.

Coagulogram: fibrinogen — 2.08 g/l, prothrombin time — 16.3 s, activated partial thromboplastin time (aPTT) — 30.4 s, thrombin time — 14.9 s, international normalized ratio (INR) — 1.35.

During observation, against the background of pathogenetically justified diet therapy and drug treatment, the child's condition improved. There was a positive dynamics of body weight gain, the peritoneal effusion and the icteric staining of the skin and sclera gradually disappeared. As a result of the treatment, motor activity was fully restored, the reaction to the examination was adequate, muscle tone in the extremities was normalized. There is puerile breathing in the lungs, the heart sounds are muffled, rhythmic, the abdomen is soft and painless on palpation, the liver is + 2.5 cm below the costal margin. The stool is mushy, yellow, the urine is light.

On abdominal ultrasound and Doppler ultrasound of the portal system in dynamics after a month of therapy: the parenchymal organs of the abdominal cavity are not changed; there are no signs of portal hypertension or hepatic vein obstruction.

In satisfactory condition, the child was discharged for follow-up with a local pediatrician, neurologist, and geneticist. Parents were given recommendations on diet therapy, the introduction of complementary foods, vitamin D3 aqueous solution 4000 IU/day was prescribed for a course of 1 month with a transition to a prophylactic dose of 1000 IU/day for a long time, ursodeoxycholic acid preparations of 15 mg/kg per day were recommended.

CONCLUSION

Galactosaemia is a serious hereditary disease caused by metabolic disorders of galactose and, as a result, lactose intolerance. The disease manifests itself in the first days of life and can be extremely difficult with the rapid development of multiple organ disorders. With the earliest possible diagnosis, timely initiation of pathogenetically justified diet therapy and its strict adherence, the prognosis for the life and development of a child with classical galactosaemia is quite favorable. The presented clinical example points out the difficulties of differential diagnosis of galactosaemia

with intrauterine infection. Screening allowed us to diagnose galactosaemia in 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.

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

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

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WILKIE SYNDROME AS A COMPLICATION OF MISDIAGNOSED CROHN'S DISEASE

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Abstract. Wilkie's syndrome or superior mesenteric artery (SMA) syndrome is a relatively rare condition due to abnormal branching of the SMA from the abdominal aorta due to the disappearance of adipose tissue that provides stability of the angle between the two major arterial vessels and, consequently, compression of the duodenum with subsequent impaired passage. The development of Wilkie's syndrome, given the data of the literature and our own experience, is always secondary. The peculiarity of our clinical case of Wilkie's syndrome in an adolescent girl is the child's prolonged treatment for misdiagnosed Crohn's disease of the colon, followed by the discovery of angiodysplasia and repeated surgical interventions, resulting in weight loss and, consequently, the development of syndrome or SMA.

Key words: *Wilkie's syndrome, superior mesenteric artery syndrome, intestinal angiomatosis, Crohn's disease.*

СИНДРОМ УИЛКИ КАК ОСЛОЖНЕНИЕ ОШИБОЧНО ДИАГНОСТИРОВАННОЙ БОЛЕЗНИ КРОНА

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Резюме. Синдром Уилки, или синдром верхней брыжеечной артерии (СВБА) — относительно редкое состояние, обусловленное аномальным отхождением верхней брыжеечной артерии от брюшного отдела аорты из-за исчезновения жировой ткани, которая обеспечивает стабильность угла между двумя крупными артериальными сосудами, и, соответственно, сдавливанием двенадцатиперстной кишки с последующим нарушением пассажа. Развитие синдрома Уилки, учитывая данные литературы и собственный опыт, всегда вторично. Особенностью нашего клинического случая синдрома Уилки у девочки-подростка является длительная курация ребенка по поводу ошибочно диагностированной болезни Крона толстой кишки, с последующими обнаружением ангиодисплазии и неоднократными оперативными вмешательствами, приведшими к потере веса и, как следствие, развитию СВБА.

Ключевые слова: *синдром Уилки; синдром верхне-брыжеечной артерии; ангиоматоз кишечника; болезнь Крона.*

INTRODUCTION

Compression of the inferior or horizontal part of the duodenum (DU) between the abdominal aorta and the superior mesenteric artery (SMA) as a cause of intestinal obstruction was first described by Karl von Rokitansky in 1861 in a post mortem case. The syndrome was later studied in detail and described by Wilkie in 1927 [1].

The syndrome has many names, the most famous of which are: Wilkie's syndrome, superior mesenteric artery (SMA) syndrome, cast syndrome and aorto-mesenteric compass syndrome. The disease is very rare with only 500 reported cases in the literature and an estimated prevalence of 0.013%-0.3% according to the upper gastrointestinal tract radiography [2, 3]. It is more common among the female than male gender at a ratio 2:1 ratio, mainly between the second and fourth decades of life [3, 4].

Wilkie's syndrome is caused by compression of the third part of the duodenum between the aorta and the superior mesenteric artery branching from it at an acute angle, which in turn, leads to duodenal obstruction. Normally, the angle between the SMA and the aorta ranges from 25 to 60°, but with this syndrome it is narrowed (from 6 to 25°). An acute aortomesenteric angle is formed due to congenital anomalies (high insertion of the ligament of Treitz, low origin of the SMA from the abdominal aorta), significant weight loss, lumbar hyperlordosis, restorative proctocolectomy with ileaoanal anastomosis and other conditions. That is, this syndrome can be caused by various reasons, ranging from congenital anomalies to a hypercatabolic state or malnutrition. As a result, there is a loss of perivascular and retroperitoneal fatty cushion, which leads to narrowing of the aortomesenteric angle and subsequent compression of the duodenum [3]. However, 40.4% of cases are idiopathic [5].

The duodenal compression can be partial or complete, acute or chronic, resulting in the appearance of completely nonspecific symptoms, the most pronounced of which are the following: postprandial abdominal pain (59%), nausea (40%), vomiting with sudden weight loss and electrolyte imbalance (50%), early satiety (32%) and anorexia (18%). Symptoms are aggravated by lying supine after eating and are relieved by assuming the left lateral decubitus, prone or knee-chest position. In addition, symptoms can be masked under more common diseases such as peptic ulcer disease, biliary colic, pancreatitis, and mesenteric ischemia. During physical examination, an asthenic body habitus in this group of patients attracts attention.

The diagnosis of Wilkie syndrome requires a high degree of clinical suspicion, supported by radiographic studies demonstrating compression of the third portion of the duodenum. Computed tomography (CT) scan of the abdomen with contrast, being the gold standard for diagnosing SMA syndrome, allows to reveal not only the acute angle of the SMA from the aorta and the distance between the compressive vessels, but also the dilation of the stomach and duodenum.

Questions about the method of treating Wilkie's syndrome still remain controversial in the world literature. In some cases, the disease responds to successful conservative in the form of adequate nutrition by enteral/parenteral feeding and proper positioning of the patient after feeds.

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Surgery is resorted to when conservative measures are ineffective or in patients with a long history of progressive weight loss or pronounced duodenal dilatation with stasis and complications [6].

We present a clinical observation of a patient in whom the onset of SMA was caused by weight loss developed as a complication of surgical diseases of the upper gastrointestinal tract, which required surgery in the form of duodenojejunostomy.

CLINICAL OBSERVATION

A 16-year-old girl was admitted to the Filatov Children City Clinical Hospital with complaints of abdominal pain after eating, bloating, nausea, belching, episodes of vomiting, and lack of weight gain.

It is known from the anamnesis that she became acutely ill at the age of eleven, when, due to an intestinal infection, abdominal pain, weakness, diarrhea, blood in stool appeared. After treatment, blood and mucus from the rectum persisted. Due to existing complaints, the girl was repeatedly examined and treated in pediatric gastroenterology departments with a diagnosis of Crohn's disease, where anti-inflammatory therapy with Pentasa was carried out for a long time with a short-term effect; massive hormonal and cytostatic therapy had a negative effect. The discharge of blood and mucus in the stool persisted. During the next aggravation (bleeding), two years after the onset of the disease, a large rectal ulcer was found, which required laparoscopic Soave–Georgeson procedure, during which the rectum with the ulcerative defect was resected. In the postoperative period, anastomotic failure was noted and a retrorectal abscess occurred, which was relieved by drainage and antibiotic therapy. Three months later, the child underwent angiography (Fig. 1), which angiodysplasia of the distal colon, and therefore re-resection of the colon with pull-through procedure and ileostomy was performed. The postoperative period was complicated by the failure of the coloanal anastomosis, the recurrence of intestinal bleeding. The child was rushed to the Istanbul clinic, where a rectovaginal fistula and intestinal bleeding were detected. The repeated Soave pull-through procedure and fistulotomy were performed. However, a complication occurred again in the form of adhesive intestinal obstruction, which was resolved surgically. Two weeks after the operation, bright red blood appeared again from the rectum colonoscopies and rectal biopsies were performed several times (Fig. 2). No evidence of Crohn's disease or other inflammatory bowel diseases was identified; the resulting morphological picture was more consistent with angiodysplasia of the colon.

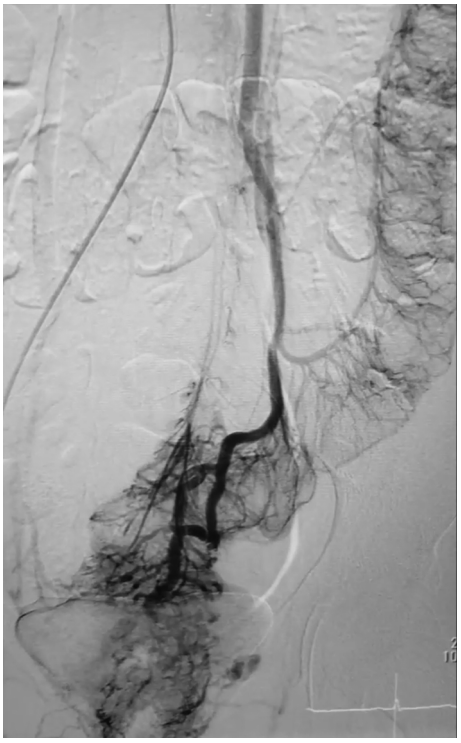

Fig. 1. Angiography showing foci of hypervascularisation in the distal colon, rapid discharge on the veins (before contrasting *V. portae*)

Рис. 1. Ангиография, на которой видны очаги гиперваскуляризаци в дистальных отделах толстой кишки, быстрый сброс на вены (до контрастирования *V. portae*)

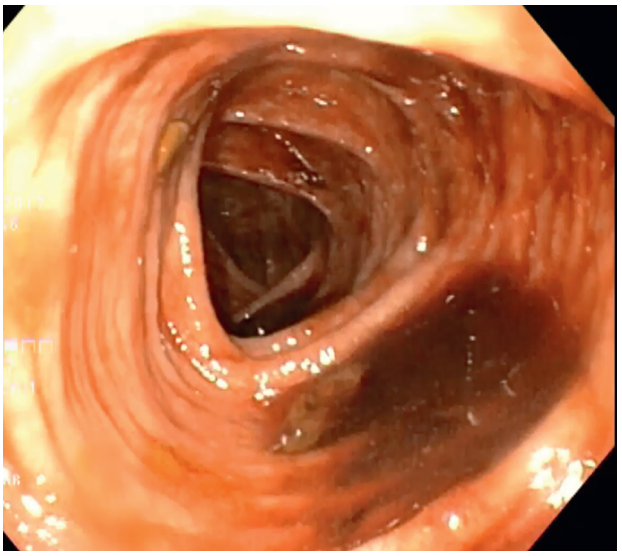

Fig. 2. Colonoscopy. Haemorrhagic content is detected in the lumen of the large intestine

Рис. 2. Колоноскопия. В просвете толстой кишки определяется геморрагическое содержимое

Over the next two months, the girl was treated at the Filatov Children City Clinical Hospital with a diagnosis of angiodysplasia of the colon; multiple ulcers of the colonic mucosa; chronic intestinal bleeding; posthemorrhagic anemia of I–II degree; ileostomy carrier; a follicular cyst of the right ovary. Operated: midline laparotomy, adhesiolysis, resection of the right ovarian cyst, colectomy. Ileorectal anastomosis, ileostomy. The postoperative period was difficult. A year later, the child underwent ileostomy closure. There were no complications. The wound healing is complete. The intestinal passage recovered in the first 24 hours. Two months later, the girl was hospitalized again in an emergency with a diagnosis of chronic ulcerative proctitis, rectovaginal fistula, intestinal bleeding. During sigmoidoscopy and vaginoscopy, a punctate fistula was identified in the vagina, communicating with the rectum in the area of the intestinal anastomosis, and therefore relaparotomy, adhesiolysis, and the end ileostomy formation were performed. The postoperative period proceeded without complications, the intestinal passage was recovered on the first postoperative (po) day.

Upon admission, the child's condition was severe due to the underlying disease. The girl has an asthenic body habitus, the skin is pale, dry in the limb area, the nails are layered, the tongue is covered with a white coating, the teeth are yellow with plaque. On the stoma — liquid small intestinal discharge. Body weight — 36 kg, height — 163 cm. The child has severe malnutrition: BMI — 13.5, average deviation from BMI — 3.69. Physical development is moderate, dysharmonious due to low body weight, the deficiency of which corresponds to the III degree of malnutrition.

Examined: an ultrasound examination of the abdominal organs (abdominal ultrasound) revealed an expansion of the duodenum up to 29 mm. The angle between the SMA and the aorta was 10°, and the diameter of the intestine in the area of the aorto-mesenteric tweezers was 2.5 mm. There were echo signs of adhesive disease, mild ascites and reactive changes in the pancreas. Esophagogastroscopy revealed gastroduodenitis and cardiac insufficiency.

According to the results of upper gastrointestinal tract radiography with barium suspension, there were the following changes (Fig. 3): the gastroesophageal reflux grade II; the stomach is hook-shaped, elongated, the lower part is sac-like dilated, located below the pectinate line, peristalsis is deep, spastic, during which the stomach

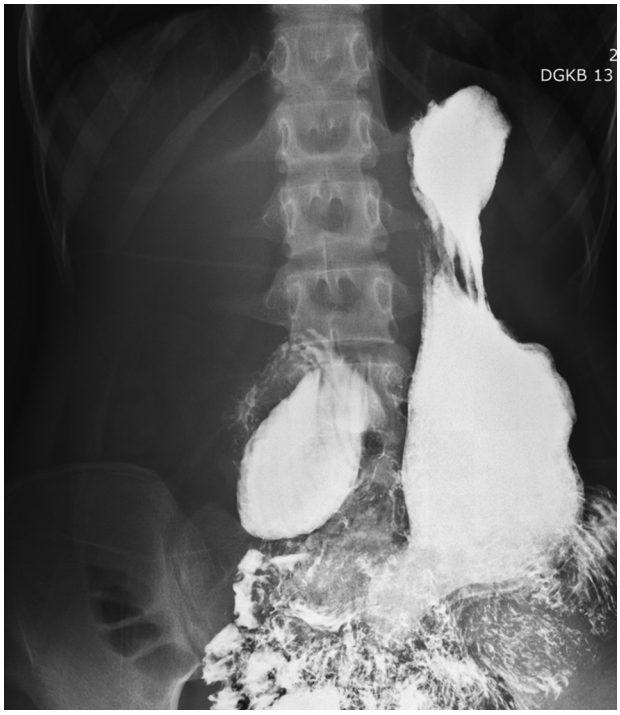

Fig. 3. The duodenum is dilated, positive "double bubble" symptom, the stomach has an hourglass shape

Рис. 3. Нижняя горизонтальная ветвь ДПК расширена, положительный симптом «двойного пузыря», желудок имеет форму песочных часов

takes the shape of an hourglass; dilatation of the lower horizontal branch of the duodenum up to 40 mm, the presence of antiperistaltic waves in it, persistent duodenogastric reflux.

After an examination by a council of doctors, a decision was made to correct protein-energy deficiency fluid and electrolyte imbalance. A course of parenteral nutrition was started under the control of basic indicators of homeostasis. However, against the background of infusion therapy, allergic reactions were observed in the form of a rash, breathing difficulty and tachycardia. Vomiting persisted during enteral load. The weight curve was without dynamics. Taking into account the above, it was decided to perform a surgical intervention on vital indications.

An operation was performed — the relaparotomy; adhesiolysis, Roux-en-Y duodenojejunostomy, enterostomy. The postoperative period proceeded without complications. Due to the severity of the condition, the child was in the intensive care unit (ICU) for 6 days, where she received partial parenteral nutrition — only protein. Upon administration of fat emulsions, the child developed a rash and itchy skin. Infusion, antibacterial, analgesic and symptomatic therapy were also carried out. There was an increase in blood amylase

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levels to 174, which required proteolytic therapy with a positive effect. On the second postoperative day, enteral feeding by enterostomy with a medical formula was started. On the same day, passage through the gastrointestinal (GI) tract was restored. On the fourth postoperative day, conservative therapy and feeding by enterostomy were continued, and at the same time, oral feeding was started. When trying to increase the rate of enteral nutrition by enterostomy, an increase in losses through the ileostomy was noted, and therefore feeding by enterostomy was stopped. The child began to eat orally with a gradual increase in the single volume of 80–100 ml. She digested the food, there was no nausea or vomiting. She was discharged on the eighth postoperative day.

Three months after the operation, the child still had reflux complaints (nausea, heartburn). When performing upper GI radiography with contrast, gastroesophageal reflux (GER) persisted, which reached stage III, while the passage was satisfactory, and during endoscopic examination there were phenomena of a catarrhal esophagitis in the lower third of the esophagus. And in endoscopic examination there were phenomena of a catarrhal esophagitis in the lower third of the esophagus. The child underwent Nissen fundoplication.

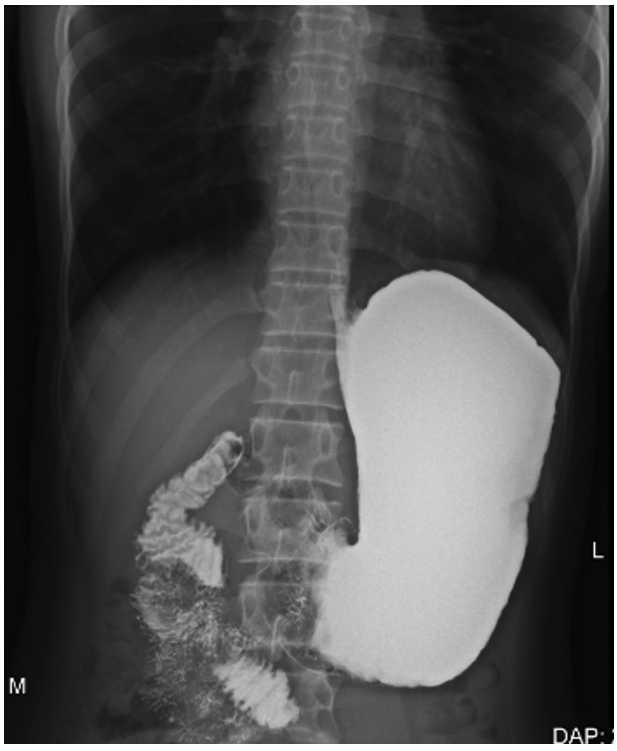

Fig. 4. The duodenum is not dilated, evacuation of contrast agent from the duodenum to the underlying sections is satisfactory, the stomach has a normal shape and size

Рис. 4. ДПК не расширена, эвакуация контрастного вещества из ДПК в нижележащие отделы удовлетворительная, желудок имеет обычную форму и размеры

After 1.5 years, the child had no complaints. According to the tested upper gastrointestinal radiography with contrast, the passage of barium from the stomach and duodenum was satisfactory, there was no gastroesophageal reflux, and the stomach had normal shape and size (Fig. 4).

Over the course of 1.5 years, the girl gained 7 kg, her weight was 43 kg. BMI — 16.2, z-score — 2.14, which corresponds to stage II malnutrition.

In addition, the patient's appetite and skin condition improved significantly, and the normal menstrual cycle was restored.

DICSUSSION

Wilkie's syndrome is characterized by a narrowing of the aortomesenteric angle (from 6 to 25°), and the distance between the compressive vessels is less than 10 mm (can be reduced to 2 mm), whereas normally it is from 10 to 28 mm [7, 8]. In a physiological state and in a straight position, the aorta-SMA angle ranges from 38 to 65° and is maintained by the presence of perivascular adipose tissue [8].

Etiological factors can be either congenital or acquired. Congenital causes include abnormally short or high insertion of the ligament of Treitz, dislocating the duodenum to a cranial position; (promoting the approach of the third part of the duodenum to the apex of the aortomesenteric angle and its compression); a low branching of the SMA from the aorta or the presence of embryonic adhesions [9]. Acquired factors may be multi-etiological. Potential causes include catabolic states such as tumors or burns, as well as diseases causing severe weight loss, such as anorexia nervosa or malabsorption syndrome. Severe trauma or lesions associated with prolonged bedtime rest like brain trauma or spinal cord have also been implied. Finally, postoperative states such as spinal surgery (cast syndrome), esophagectomies, or abdominal aorta aneurism repairs can also be in the genesis of this syndrome [9].

Regardless of the associated factors, a depletion of the fatty cushion in the area of the aorto-mesenteric tweezers occurs, leading to the anatomical changes, mentioned above.

In our case, the patient had a prolonged history without the identification of a specific trigger. She had no history of psychiatric disorders lea-

ding to weight loss, but had major past surgeries or conditions that resulted not only in severe malnutrition but also lengthy bedtime rest.

Patients with SMA syndrome may present in the acute period, with chronic insidious symptomatology or with an acute exacerbation of a chronic disease [10]. The acute form is usually less common and is characterized by signs and symptoms of intestinal obstruction, which quickly resolves with conservative therapy. As a rule, these patients experience a severe loss of body weight (within 1–2 months), and therefore have a positive response to the therapy. Chronic cases may present with progressive, non-specific symptoms that may last for years. The most commonly reported symptoms are long-term abdominal pain, nausea, vomiting bile or food content, vague postprandial indisposition, early satiety, regurgitation, food intolerance, and lack of weight gain or loss weight are the most commonly referred [9]. Persistent vomiting can also lead to dehydration, severe hypovolemia, oliguria, electrolyte imbalances such as hypokalemia and metabolic alkalosis, and ultimately the development of Mallory-Weiss syndrome [9]. Symptoms can aggravate with meals and prone position and relieved with the knee-elbow position or lateral left decubitus[1].

These symptoms may also mimic other diseases such as pancreatitis, peptic ulcers, retroperitoneal or duodenal tumors, eating disorders, or diseases characterized by slow peristalsis such as dermatomyositis or systemic lupus erythematosus [5, 9]. On physical examination, the signs are usually unclear: the abdomen is soft, accessible to deep palpation, abdominal distension and high-pitched bowel sounds are detected [8], which was not the case in our patient.

Due to the low specificity of signs and symptoms, clinical diagnosis requires a high index of suspicion, especially in patients with postprandial pain, vomiting and severe weight loss [11]. Thus, diagnosis is made based not only on clinical evidence but also on radiological findings.

The diagnostic testing of any intestinal obstruction usually begins with a plain abdominal radiography with contrast. The upper gastrointestinal tract radiography with barium reveals such pathognomonic signs of SMA syndrome as dilatation of the lower horizontal branch of the duodenum; a clear cut line that demarks the obliteration of the duodenal lumen by the superior mesenteric artery; pendulum movement of contrast agent proximal to the obstruction; delay of 4 to 6 hours in gastroduodenal transit time, with relief of the obstruction when the patient is placed in the knee-chest position, left lateral decubitus, or with the Hayes maneuver [1, 8–10]. Fibroesophagogastroduodenoscopy (FEGDS) of the upper gastrointestinal tract is usually performed to exclude an intrinsic mechanical bowel obstruction. The only symptom of SMA syndrome during endoscopy of the upper gastrointestinal tract is an extrinsic regular and sometimes pulsatile compression of the duodenal wall in the transition in the middle and lower third. FEGDS does not have high diagnostic accuracy, specificity and sensitivity and, and usually allows the detection of secondary inflammatory changes, which gives a complex view of the disease, as well as on the basis of the identified endoscopic changes allows to develop a set of measures for preoperative preparation and the postoperative period. However, abdominal multi-slice computed tomography (MSCT) scan with intravenous contrast is the gold standard of diagnosis [8], allowing to determine the aortomesenteric angle and the distance between the compressive vessels, extent of duodenal distension and exact point of obstruction, assess of the amount of retroperitoneal fat and exclude other frequent causes of intestinal obstruction (tumors, annular pancreas, aneurysms, etc.) [1, 4].

The purpose of the treatment is to interrupt the pathological cascade composed of weight loss, loss of retroperitoneal fat, narrowing of the aortomesenteric angle, external duodenal compression. Most authors believe that patients with a short period of illness, mild symptoms and incomplete duodenal obstruction should be offered conservative medical treatment [1]. Such measures include insertion of a nasogastric tube for gastric decompression, correction of electrolyte disturbances, and provision of nutrition in the form of a high-calorie oral diet if tolerated, and parenteral nutrition if necessary. The diet can be supplemented with postural maneuvers and means that improve intestinal motility [10].

Surgical intervention is indicated in cases of conservative treatment failure, a prolonged disease with progressive weight loss, and recurrent upper gastrointestinal symptoms (at least once per week for more than six months). The presence of secondary complications such as peptic ulcers and pancreatitis due to biliary reflux against the background of duodenal hypertension is also a reason

for choosing a surgical approach [1, 8–9]. To date, no period has been established during which it would be possible to determine the ineffectiveness of drug treatment [10]. No time limit has yet been set to determine the medical treatment's ineffectiveness [10]. However, some studies report failure rates of 50–70% [1]. The authors came to the conclusion that the severity of the existing symptoms and the presence of secondary complications cannot be corrected in a timely manner using a conservative method, which significantly worsens the patient's quality of life. In such situations, surgical treatment is most appropriate. The operative options include Strong's procedure, gastrojejunostomy, and duodenojejunostomy [5]. Strong's procedure is preferably used in the pediatric population and consists of lysing the ligament of Treitz allowing for mobilization of the duodenum. Although the Strong's procedure is simpler and less invasive than alternatives (no anastomoses are required), it has a high failure rate of 25% [10].

Gastrojejunostomy allows for gastric decompression, but does not eliminate duodenal (DU) obstruction [4]. This method of surgical intervention for chronic duodenal obstruction (CDO) is non-physiological and carries a large percentage of failures and complications: stomach peptic ulcers as a result of biliary reflux, and recurrence of symptoms due to non-decompression of the duodenum, the development of blind loop syndrome, etc. [1, 10]. It is used extremely rarely, and, as a rule, in patients who have previously been repeatedly operated on for CDO, when traditional methods of surgical treatment were not successful.

Duodenojejunostomy was first introduced by Starley in 1910 and over the years it is has become the most frequent treatment with a success rate of 90% [1, 12, 13]. The use of open and laparoscopic approaches has been previously reported, with the latter having advantages such as shorter hospital stay, less trauma and good cosmetic effect [5]. The first laparoscopic duodenoneuneustomy was described in 1998 by Gersin and Heniford, who proved it to be a safe and reproducible technique [9]. As noted by Escaño et al. in their case series analysis, laparoscopic duodenojejunostomy is an effective minimally invasive treatment, with an acceptable rate of postoperative complications and favorable long-term results [6]. This is why it is considered the treatment of choice. In this case, the procedure was performed uneventfully, provided immediate symptomatic relief and significantly improved the patient's quality of life.

CONCLUSION

Wilkie's syndrome poses a really challenging diagnostic task due to its rarity and non-specific symptoms. A high index of suspicion in cases of severe weight loss and upper gastrointestinal symptoms is of utmost importance. Intravenous contrast-enhanced computed tomography is the gold standard for diagnosing SMA syndrome and should be performed in all patients with radiological features of duodenal obstruction at the level of its lower horizontal branch. Early detection can not only avoid the syndrome-associated complications but also improve the prognosis, making conservative measures more likely to be effective. Surgical intervention should be considered in more severe, chronic cases or whenever medical treatment fails. Laparoscopic duodenojejunostomy has proven to be the best modality of choice warranting the best outcomes with a good safety profile. If this group of patients has severe gastroesophageal reflux grade III and esophagitis that are not amenable to conservative therapy, duodenojejunostomy must be supplemented with fundoplication.

ADDITIONAL INFORMATION

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

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

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Consent for publication. Written consent was obtained from the patient's legal representatives 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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DOCTOR OF MEDICAL SCIENCES, PROFESSOR KONSTANTIN ALBERTOVICH SHAPOVALOV IS 70 YEARS OLD

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ДОКТОРУ МЕДИЦИНСКИХ НАУК, ПРОФЕССОРУ КОНСТАНТИНУ АЛЬБЕРТОВИЧУ ШАПОВАЛОВУ — 70 ЛЕТ

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On March 14, 2024, research physician, Doctor of Medical Sciences, Professor Konstantin Albertovich Shapovalov celebrates his 70th birthday.

Konstantin Albertovich graduated from the medical faculty of Arkhangelsk State Medical Institute (ASMI) and completed his clinical residency at the Department of General Surgery in ASMI. He combined his studies with an outpatient pediatric surgery practice. Later on he worked as a surgeon and a board surgeon at the Arkhangelsk Clinical Regional Hospital. Simultaneously he worked at the Arkhangelsk State Pedagogical Institute at the department of "Foundations of Medical Knowledge and Protection of Children's Health" as a teacher of surgical diseases.

Studying in ASMI, Konstantin Albertovich was actively engaged in scientific circles of the departments of topographic anatomy and operative surgery, social sciences, naval training and hospital surgery since the second year. He prepared 10 reports for student scientific conferences (5 in co-authorship). He continued scientific researches in clinical residency. He fulfilled and successfully defended dissertations for the degrees of PhD and MD.

After moving to Syktyvkar town, Konstantin Albertovich was engaged in teaching and research work, not breaking the connection with practical medicine. He worked at the Komi State Pedagogical Institute as a senior lecturer, associate professor, head of the department "Foundations of Medical Knowledge and Protection of Children's Health". Simultaneously, he worked as a pediatric surgeon in Syktyvkar Children's Polyclinic No. 3.

In accordance with the decision of the Ministry of General and Professional Education of the Russian Federation from 28.01.1997 № 40-d Konstantin Albertovich Shapovalov was awarded the academic rank of associate professor in the department "Fundamentals of Medical Knowledge and Child Health Protection".

By the resolution of the Ministry of Education of the Russian Federation from 16.02.2000 № 52-p — he received the academic rank of professor in the department "Basics of medical knowledge and protection of children's health".

Konstantin A. Shapovalov is the author of 520 scientific and educational-methodical publications. The total volume of personal contribution is 422,96 conventional author's sheets, including 355 scientific (257,20) and 165 educational-methodical (165,76) works, including 10 monographs and 12 manuals. For the last 3 years 77 works have been published. The total volume of personal contribution amounted to 38,71 conventional author's sheets.

MD, Professor Konstantin A. Shapovalov is the scientific director of the project "Topical issues of outpatient, polyclinic and consultative pediatric medical care in the Komi Republic". The health

status of the contingent attached to Syktyvkar Children's Polyclinic No. 3 is studied on the basis of analysis and generalization of information on the contingents:

- children with disabilities — identification of disabilities in children and adolescents; reasons that cause initial disability; terms of re-examination for initial disability; diseases that caused the onset of disability; main health disorders; leading limitations of life activity; structure of rehabilitation measures; morbidity; medical and rehabilitation measures; sanatorium and resort treatment; results of re-examination; individual rehabilitation program for disabled children; monitoring of the quality of rehabilitation programs for children with disabilities.
- children with "14 nosologies" and orphan diseases included in the regional segment of the federal register;

and sections:

- "lean outpatient clinic";
- standard of the workplace of a primary pediatrician;
- organization of medical support for the fulfillment of the standards of the National Physical Culture and Sports Complex "Ready for Labor and Defense";
- pediatrics of catastrophes;
- personnel work;
- internal quality control of medical care.

Scientific work in a practical medical and preventive institution providing primary health care is an obligatory part of the certification work of a doctor for awarding a qualification category. Its analysis broadens the outlook of a practical doctor, shows the place of departments in the results of treatment. The following scientific projects become the platforms for discussion of abstracts of the obtained results of the Project section: 8th Europaediatrics Congress jointly held with The 13th National Congress of Romanian Pediatrics Society, June 7–10, 2017, Palace of Parliament, Bucharest, Romania; XXI Congress of Pediatricians of Russia with international participation "Actual problems of pediatrics", February 15–17, 2019, Moscow, RF; 9th Europaediatrics Congress, June 13–15, Dublin, Ireland; XXII Congress of Pediatricians of Russia with international participation "Actual problems of pediatrics", February 21–23, 2020, Moscow, Russia; IV National Congress with international participation "Healthy children — the future of the country", October 28, 2020, St. Petersburg, Russia; XXIII Congress of Pediatricians of Russia with international participation "Actual problems of pediatrics", March 5–7, 2021, Moscow, Russia; IX International Congress "ORGZDRAV-2021. Effective Management in Healthcare", May 25–27,

2021, Moscow, Russia; V National Congress with international participation "Healthy Children — the Future of the Country", May 26–28, 2021, St. Petersburg, Russia; XIX Congress of Pediatricians of Russia with international participation "Actual Problems of Pediatrics", March 5–7, 2022, Moscow, Russia; VI National Congress with international participation "Healthy Children — the Future of the Country", June 1–2, 2022, St. Petersburg, Russia; XI International Congress "ORGZDRAV-2023. Effective Management in Healthcare", June 7–9, 2023, Moscow, Russia; VII National Congress with international participation "Healthy Children — the Future of the Country", June 15–16, 2023, St. Petersburg, Russia.The results of the Project's research have been published in such Russian scientific and practical journals as: "Yakutsk Medical Journal"; "Medicine: Theory and Practice", "Russian Pediatric Journal", "Pediatric Bulletin of the South Urals", Children's Medicine of the North-West, Forcipe, "ORGZDRAV: News, Opinions, Training, "Vestnik VSHOUZ", as well as foreign scientific and practical journals: "Pediatrics. Eastern Europe"; Archives of Disease in Childhood; Journal of Advanced Pediatrics and Child Health; Open Journal of Pediatrics and Child Health; Journal of Pediatrics and Neonatal Medicine.

We warmly congratulate Konstantin Albertovich with his 70th birthday! We wish you further fruitful scientific work for the benefit of children's health. Always remain a bright ray of knowledge, progress and prosperity. Let every new day give you a lot of positive emotions, inspiration for new aspirations and achievements. We wish you love of your relatives, support of colleagues, respect of others and good luck in your destiny.

ПРАВИЛА ДЛЯ АВТОРОВ

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

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

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

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В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

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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.

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Статья должна иметь **(НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ)**:

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Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Children's medicine of the North-West» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

Рекомендуемая структура аннотации: введение (Background), цели и задачи (Purposes and tasks), методы (Materials and methods), результаты (Results), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. Объем текста авторского резюме определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах 200–250 слов (1500–2000 знаков).

4. **Ключевые слова** (Key words) от 3 до 10 ключевых слов или словосочетаний, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «ключевые слова». Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом

списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются точкой с запятой.

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

6. **Литература** (References). Список литературы должен представлять полное библиографическое описание цитируемых работ в соответствии с NLM (National Library of Medicine) Author A.A., Author B.B., Author C.C. Title of article. Title of Journal. 2005;10(2):49–53. ***Список формируется в порядке упоминания источников*** (если источник упоминается несколько раз, то используется номер ссылки первого упоминания). В описании указываются ВСЕ авторы публикации. Библиографические ссылки в тексте статьи даются цифрой в квадратных скобках. Ссылки на неопубликованные работы не допускаются.

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

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

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

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

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

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

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

Статья из журнала

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

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

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

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/ 47/. (accessed 11.09.2013).

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

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

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

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика.

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

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

2. Копируем транслитерированный текст в готовящийся список References.

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

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

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

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи

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

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

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

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

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

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

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

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

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

Авторефераты

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

Описание Интернет-ресурса

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

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

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

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

Объем рукописей.

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

Иллюстрации и таблицы. Число рисунков рекомендуется не более 5. В подписях под рисунками должны быть сделаны объяснения значений всех кривых, букв, цифр и прочих условных обозначений. Все графы в таблицах должны иметь заголовки. Повторять одни и те же данные в тексте, на рисунках и в таблицах не следует. **Все надписи на рисунках и в таблицахприводятся на русском и английском языках.**

Рисунки, схемы, фотографии должны быть представлены в точечных форматах tif, bmp (300–600 dpi), или в векторных форматах pdf, ai, eps, cdr. При оформлении графических материалов учитывайте размеры печатного поля Журнала (ширина иллюстрации в одну колонку — 90 мм, в 2 — 180 мм). Масштаб 1:1.

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

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АДРЕС РЕДАКЦИИ

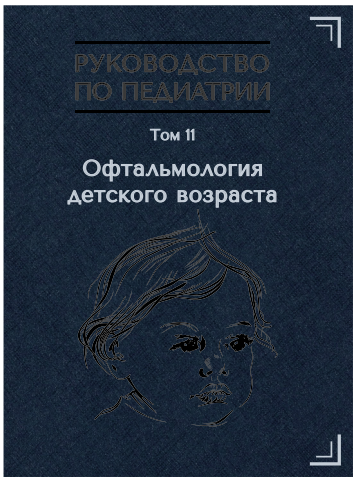
194100, Санкт-Петербург, Литовская ул., 2
e-mail: lt2007@inbox.ru.

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

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

Руководство по педиатрии. ОФТАЛЬМОЛОГИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.В. Бржеский



Том 11 «Руководства по педиатрии» отражает современный уровень развития офтальмологии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний глаз у детей. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Издание предназначено офтальмологам, педиатрам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

Твердый переплет, цветные иллюстрации, 344 страницы.

Приобрести издание можно в интернет-магазине Лабиринт:
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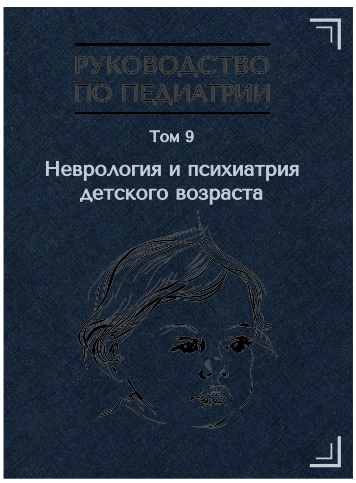
Руководство по педиатрии. НЕВРОЛОГИЯ И ПСИХИАТРИЯ ДЕТСКОГО ВОЗРАСТА

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



Том 9 «Руководства по педиатрии» отражает современный уровень развития неврологии и психиатрии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний нервной системы и психических расстройствах. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Руководство предназначено неврологам, нейрохирургам, психиатрам, психотерапевтам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

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